COMPARISON OF ISOFLURANE ALONE WITH ISOFLURANE AND N ACETYL CYSTEINE ON THE POSTOPERATIVE LIVER FUNCTIONS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA

A STUDY OF 60 CASES

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH X (ANAESTHESIOLOGY)

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DR.M.G.R MEDICAL UNIVERSITY

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This is to certify that this dissertation entitled "**COMPARISON OF ISOFLURANE ALONE WITH ISOFLURANE AND N ACETYL CYSTEINE ON THE POSTOPERATIVE LIVER FUNCTIONS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA**" submitted by **DR.S.MADHANA GOPALAN** to the FACULTY OF ANAESTHESIOLOGY, THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement in the award of the degree of M.D., degree Branch X (ANAESTHESIOLOGY) for the April 2015 examination is a bonafide research work carried out by him under my direct supervision and guidance.

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DECLARATION

I, **DR.S.MADHANA GOPALAN** declare that the dissertation titled "**COMPARISON OF ISOFLURANE ALONE WITH ISOFLURANE AND N ACETYL CYSTEINE ON THE POSTOPERATIVE LIVER FUNCTIONS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA**" has been prepared by me. This is submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the requirement for the award of **M.D. Degree Branch X (Anaesthesiology)** Degree Examination to be held in **April 2015.** I also declare that this dissertation, in part or full was not submitted by me or any other to any other university or board, either in India or abroad for any award, degree or diploma

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CONTENTS

ABSTRACT

COMPARISON OF ISOFLURANE ALONE WITH ISOFLURANE AND N ACETYL CYSTEINE ON THE POSTOPERATIVE LIVER FUNCTIONS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA - A STUDY OF 60 CASES

AIM : This study was undertaken with the aim of prospectively comparing the effects of isoflurane and N acetyl cysteine with isoflurane on liver functions in patients undergoing laparoscopic surgeries under general anesthesia.

MATERIALS AND METHODS: It was a prospective randomized controlled double blinded study. Sixty ASA I and II patients in age group 18 – 60 years scheduled for elective laparoscopic surgeries under general anaethesia were included in the study. Patients undergoing laparoscopic appendicectomy and hernioplasty were included. The patients were allocated into two groups in a randomized manner. **GROUP P** (Placebo group) patients were given Isoflurane with normal saline and **GROUP N** (N acetyl cysteine group) were administered N acetyl cysteine with isoflurane. In a randomized manner 30 patients were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline(Group N) while 30 patients received only 250 ml of 0.9% normal saline(Group P) before induction.Both the groups were induced with a standard intravenous induction technique. Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen with 1-2% isoflurane in fresh gas flow of 6 l/min. The parameters observed in preoperative period postoperative 1st hr and postoperative 24th hr from peripheral venous blood were Serum bilirubin, Aspartate aminotransferase, Alanine aminotransferase, Lactate dehydrogenase, Prothrombin time. Perioperative

side effects were also noted. The differences between the two groups were tested by unpaired t test.A p value of <0.05 was considered statistically significant.

Results : Patient characteristics were comparable in both the groups.Bilirubin and prothrombin time did not significantly change in the two groups at postoperative period. Alanine aminotransferase levels showed a little decrease in both groups during postoperative 1st hour but not statistically significant. Lactate dehydrogenase levels did not show any significant difference in both the groups. Aspartate aminotransferase levels were increased in both the groups during the postoperative period but was not statistically significant. (p value >0.05).

Conclusion : Liver functions are well preserved in patients receiving isoflurane alone and in patients receiving isoflurane with N-acetyl cysteine. Hence infusion of N-acetyl cysteine does not offer any benefit in patients receiving isoflurane anaesthesia.

INTRODUCTION

The general anesthetics were introduced into clinical practice over 150 years ago. It is one of the greatest milestone achieved in the field of medicine. This discovery revolutioned the branch of anaesthesiology. It has helped the specialty of modern surgery to flourish beyond imagination.

General anesthesia can broadly be defined as a drug-induced reversible depression of the central nervous system resulting in the loss of response to and perception of all external stimuli. A dynamic balance between the level of hypnosis, analgesia and stimulation is general anaesthesia. It is usually defined as a triad of amnesia, analgesia and muscle relaxation.

Inhalation anaesthetics are the most common drugs used for general anesthesia. A state of unconsciousness and amnesia is achieved by adding inhaled anaesthetic to inspired oxygen. A fraction of inhaled agent is enough to produce anaesthesia. A balanced anaesthesia is achieved when combined with intravenous anaesthetic agents, opioids and benzodiazepines and results in still deeper plane. Ease of administration and monitoring the clinical effects of inhaled agents and reliable measurement of their end tidal concentration has given way to the

widespread use of inhaled anaesthetics. In addition, volatile anesthetic gases are relatively inexpensive in terms of the overall cost.

Predictable intraoperative and recovery profile makes the volatile anaesthetic agents the most commonly used agents for maintenance of general anesthesia. Maintenance of haemodynamic status of the patient and rapid recovery is the greatest advantage of volatile anaesthetics. They play a vital role in performing a balanced anaesthesia.

Rapid induction and recovery may lead to faster operating room turnover times; shorter recovery room stays, and earlier discharges to home.

Various organ and system toxicities are seen with volatile anaesthetics since they have become operational. Since they are metabolized in the liver, hepatic toxicity is one of the most vital adverse effect . Halothane anaesthesia is related to postoperative hepatitis ranging from mildly elevated bilirubin levels to fatal fulminant hepatic necrosis. Isoflurane is metabolized very little in liver (0.17%) and is safer than halothane. There are some reports of hepatitis due to isoflurane anaesthesia but not severe as in halothane cases. These agents are not toxic themselves, their by-products or end products of metabolism are toxic. Isoflurane is halogenated ether and an isomer of enflurane. Its anaesthetic induction is faster and is nearly insoluble in blood. Only 0.17% of isoflurane is metabolized in liver

and produce trifluoroacetic acid. Trifluoroacetic acid is a reactive metabolite and main reason for hepatic toxicity. Trifluoroacetic acid binds to hepatocyte proteins and acts like a hapten. These antigens are attacked by patients antibodies.

The toxicity of volatile anaesthetics can be seen after biodegradation. Biodegradation causes lipid per oxidation and depletion of antioxidants like glutathione.

The purpose of this study is to assess the antioxidant effects of N acetyl cysteine which replaces the depleted glutathione stores caused by biodegradation in patients undergoing surgery with isoflurane anaesthesia.

AIM OF THE STUDY

This study was undertaken with the aim of prospectively comparing the effects of isoflurane and N acetyl cysteine with isoflurane on liver functions in patients undergoing laparoscopic surgeries under general anesthesia.

HISTORY

The speciality of anaesthesia rests on discoveries made from several scientific disciplines. Major discoveries were often made by small groups of curious individuals with diverse backgrounds.

Ethyl ether was first created in a laboratory by a German scientist named Valerius Cordus in 1540. Joseph Priestly discovered N_2O in 1773. Sir Humphrey Davy experimented with N_2O and reported loss of pain, euphoria in 1798.He called it as “laughing gas”.

In 1824 Henry Hill Hickman demonstrated that surgical procedures can be carried out using anesthesia with carbon dioxide and introduced the concept of anesthesia using an inhaled substance.In 1842 Crawford W. Long first used diethylether for neck surgery. He did not publicize, in part because of concerns about negative fallout from “frolics”.

Nitrous oxide was used by Horace Wells for tooth extraction in 1844. In 1846 W T G Morton (apprentice under Horace Wells) successfully induced anesthesia using ether administration on October 16 at the Massachusetts General Hospital. It was for the first time, anaesthesia was successfully demonstrated before public .

In 1847 David Waldie at Edinburgh Medical school England suggested Chloroform as an alternative agent.

In 1853 Chloroform got its royal approval when Queen Victoria was anaesthetized with chloroform during birth of Prince Leopold. Chloroform had a advantage of pleasant odour and nonflammability. The major disadvantages of chloroform were its ability to cause severe cardiovascular depression and dose related hepatotoxicity.

The general anesthetic effects of trichloroethylene were described by Lehmann in 1911.Cyclopropane was discovered accidentally in 1929 by Lucas and Henderson in Toronto and cyclopropane was very popular for almost 30 yrs. The production of a nonflammable agent was very neccessary because of increased risk of fire accidents due to usage of electronic machines

In 1932, Booth and Bixby observed that the substitution of other halogens with fluoride reduces boiling point and increases the stability of gases. Fluroxene was the first fluorine containing anesthetic agent. In concentrations greater than 3% it is explosive.

In 1951 Halothane was synthesised by Suckling and introduced into clinical practice in 1956 by Michael Johnstone in Manchester.In 1960 Methoxyflurane was introduced and withdrawn due to its nephrotoxic potential.

Between 1959 & 1966 R C Terrell and colleagues at Ohio medical products synthesised more than 700 products. Enflurane & Isoflurane

were the 347th and 469th compound respectively. Enflurane is a halogenated methyl ethyl ether. Isoflurane is the structural isomer of enflurane . Purification of isoflurane is complicated and it was suspected to be cardiotoxic which delayed its introduction till 1981.

R F Wallin and colleagues at Travenol laboratories synthesized Sevoflurane in 1970. Sevoflurane was introduced into clinical practice initially in Japan.

Desflurane was produced by Dr Ross Terrell.It is an fluorinated methyl ethyl ether. It is a volatile anaesthetic with the properties of cyclopropane without its flammable nature.

MECHANISM OF ACTION

Certain theories of mechanism are Meyer Overton theory of Lipid solubility, alterations to lipid bilayers like lipid perturbation dimensional change, lipid phase transition - "lateral phase separation", lipid-protein interactions and alteration to Protein Function like luciferase inhibition. The unitary theory of narcosis states that all anaesthetic agent have a common mechanism of action on a specific molecular site.

Meyer and Overton's olive oil:gas partition coefficient has better correlation with anaesthetic potency . The product of the partial pressure of anaesthetizing gas and the oil:gas partition coefficient varies very little over a wide range of anaesthetising partial pressures. This is species dependent, and in humans is,

$$PGas \times tO:G \sim 1.28 \pm 0.09 \text{ bar}$$

The outstanding closeness of this relationship suggests a unitary molecular site of action and when a critical number of anaesthetic molecules occupy a specific hydrophobic site in the central nervous system, it results in anaesthesia .

This relationship has led to questions about explanation for the molecular basis in cellular hydrophobic sites. As per Meyer-Overton rule the number of anaesthetic molecules which occupy the site of action is important and not the type of anaesthetic molecules. This hypothesis explains the additive characteristics of anaesthetic drugs.

There are certain limitations to the Meyer-Overton Rule. Though isoflurane is a structural isomer of enflurane and have oil:gas partition coefficients in similar range , the minimum alveolar concentration for isoflurane is considerably low than that for enflurane. Other factors influencing the potency of anaesthetic agents are considered to be the reason for difference between the two agents. Some factors affecting the potency are complete halogenation of alkane or ether reduces the potency and increase the convulsant activity, the cut off effect and the action on specific receptors like opiod receptors.

L. Pauling & S. Miller by 1961 suggested that the clatharates of water formed in cell membranes and anaesthetic molecules acting as seeds for crystals of water can be the possible mechanism of action of anaesthetic agents. They make changes in the membrane ion transport by formation of water clatharates.The potency of anaesthetic agent is related to change in surface tension as postulated by Clements and Wilson (1962). Meyer Overton theory does not explain why anaesthesia occurs. Critical volume hypothesis by Mullins (1952) states that the anaesthetic potency correlates with lipid solubility and molar volume. When the hydrophobic region is expanded beyond a particular critical volume,it results in anaesthesia. But all lipid soluble agents are not anaesthetics.

MINIMUM ALVEOLAR CONCENTRATION (MAC)

Eger and colleagues suggested this measure of Minimum alveolar concentration. It is the best estimate about anaesthetic potency of volatile agents.

MAC represents alveolar concentration of an inhaled anaesthetic at 1 atm pressure in 100%Oxygen at equilibrium, that produces immoblity in 50% of those subjects exposed to a standardized noxious stimuli. Surgical skin incision is the usual stimulus used in humans for determination of MAC. In animals it is usually produced by clamping of tail or passing electric current through subcutaneous electrodes. The alveolar concentration of anaesthetic agents can be readily measured . The alveolar and brain tensions of anaesthetic agents are approximately same. This makes minimum alveolar concentration a better measure of anaesthetic potency. Rapid equilibration is achieved by the high cerebral blood flow. Movement in about 95 percent of the patients is prevented by 1.3 times the minimum alveolar concentration. It mirrors brain partial pressure after a period of equilibration.

MAC does not vary with a variety of noxious stimuli. There may be a small individual variability. Sex, height, weight & duration of anaesthesia do not change minimum alveolar concentration. Increase in MAC is seen in hyperthermia, hypernatraemia, chronic alcohol abuse.

Decrease in MAC:

Hypothermia, Increasing age, Pre-operative medication, Drug-induced decreases in central nervous system catecholamine levels, Alpha-2 agonists, Acute alcohol ingestion , Pregnancy, Postpartum, Lithium, Lidocaine, neuraxial opioids, Ketanserin, P_{ao2} < 38 mm Hg, Blood pressure < 40 mm Hg, Cardiopulmonary bypass, Hyponatremia.

No change in MAC:

Anaesthetic metabolism, Chronic alcohol abuse, Gender, Duration of anaesthesia, P_{aco2} 15 to 95 mm Hg, P_{ao2} > 38 mm Hg, Blood pressure > 40 mm Hg, Hyperkalemia or hypokalemia, Thyroid gland dysfunction.

MAC awake- MAC of anaesthetic that would allow opening of eyes on verbal commands during emergence from anaesthesia (0.3-0.4 MAC)

MAC Intubation -MAC of anaesthetic needed to prevent movement and coughing at the time of intubation with endotracheal tube (1.3 MAC).
MAC Bar-MAC of anaesthetic needed to prevent adrenergic response to skin incision, as measured by serum levels of catecholamine in venous blood (1.5 MAC)

Mechanism of Immobility:

MAC is based on the characteristic ability of inhaled drugs to produce immobility by virtue of actions of these drugs principally on the spinal cord rather than on higher centers. The observation that immobility during noxious stimulation does not correlate with electroencephalographic activity reflects the fact that cortical electrical activity does not control motor responses to noxious stimulation. Effects of inhaled anaesthetics on the spinal cord leading to immobility or diverse and likely reflect drug induced depression of excitation as well as enhancement of inhibition. In this regard, inhaled anaesthetics depress excitatory alpha-amino-3 AMPA and NMDA receptor-mediator currents by actions independent of inhibitory $GABA_A$ and glycine receptor-mediated currents. Actions on sodium ion channels but not potassium channels may also be important in producing immobility. Conversely, cholinergic receptors do not seem to exert a significant role in anaesthetic induced immobility at the spinal cord level. Likewise, although opioids and stimulation of $alpha_2$ adrenergic receptors decrease MAC, it is unlikely that immobility produced by inhaled anaesthetics is due to activation of these receptors. Inhaled anaesthetics do not act via opioids receptors. Overall, no inhaled anaesthetic action on a single group of receptors can explain immobility

and immobility as a result of concurrent actions on many receptors is unlikely.

Ionotropic and Metabotropic Receptors:

Two families of receptors involved in neurotransmitter signaling are labelled as ionotropic and metabotropic receptors. Ionotropic receptors are also known as ligand-gated ion channels because the neurotransmitter binds directly to ion channel proteins and this interaction causes opening of the ion channels allowing transmission of specific ions causing alterations in membrane potentials. Ionotropic receptors consists of several sub-units and each sub-unit consists of four transmembrane segments. Metabotropic receptors vary from ionotropic receptors. Metabotropic receptors are monomeric receptors comprising of seven transmembrane segments. Neurotransmitters binds with metabotropic receptors and causes activation of guanosine triphosphate binding proteins associated with the receptors and these G-proteins functions as second messengers to activate other signaling molecules such as protein kinases.

Inhaled anaesthetics do not seem to stimulate the release of endogenous opioids and autonomic or ventilatory reflexes to noxious stimulation are not suppressed at concentrations that suppress movement. The fact that small doses of opioids decrease MAC reflects their ability to provide an effect that is not present with inhaled anaesthetics alone.

Evidence that alpha$_2$ receptors participate in the immobility produced by inhaled anaesthetics is provided by decreases in MAC produced by clonidine although alpha$_2$ adrenergic receptors are not considered to mediate the capacity of inhaled anaesthetics to produce immobility. A small portion of the ability of inhaled anaesthetics to produce immobility may be mediated by 5-HT receptors.

Inhibitory Ligand-Gated and Voltage Gated Channels:

Glycine receptors are major mediators of inhibitory neurotransmission in the spinal cord and mediate portion of the immobility produced by inhaled anaesthetics. Their spinal localization and potentiation by volatile anaesthetics is consistent with immobility as defined by MAC. Intravenous and intrathecal administration of strychnine, a glycine receptor antagonist increase MAC. Although $GABA_A$ receptors mediate immobility produced by injected anaesthetics, there is a evidence that $GABA_A$ receptors do not mediate immobility produced by inhaled anaesthetics. In this regard, the enhancing effects of inhaled anaesthetics on $GABA_A$ receptors minimally influence MAC.

Glutamate:

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system. Glutamate receptors consists of G-protein coupled

receptors and the ligand-gated receptors (NMDA, AMPA and Kainate). NMDA receptors likely are important mediators of the immobilizing effects of inhaled anaesthetics. AMPA receptors mediate the initial component of excitatory postsynaptic transmission and are likely targets for volatile anaesthetic-induced immobility. Kainate receptors are a subtype of ionotropic glutamate receptors although the importance of these receptors on MAC is unclear.

FACTORS AFFECTING UPTAKE & DISTRIBUTION

Concentration Effect

The rate of rise in arterial tension is higher with increased inspired concentration of the anaesthetic. The impact of PI(partial pressure of inhaled gas) on the rate of rise of the P_A of an inhaled anaesthetic is known as the concentration effect. The concentration effect states that the higher the PI, the more rapidly the P_A approaches the PI. The higher PI provides anaesthetic molecule input to offset uptake and thus speeds the rate at which the P_A increases. The concentration effect results from a concentrating effect and an augmentation of tracheal inflow. The concentrating effect reflects concentration of an inhaled anaesthetic in a smaller lung volume due to uptake of all gases in the lung. At the same time anaesthetic input via tracheal inflow is increased to fill the space produced by uptake of gases.

Second-Gas Effect:

The Second-Gas effect shows the ability of high-volume uptake of one gas to accelerate the rate of increase of the P_A of a concurrently administrated companion gas. For example, the initial large volume uptake of nitrous oxide accelerates the uptake of companion gases such as oxygen and volatile anaesthetics. This rapid uptake of second gas reflects increased tracheal inflow of all the inhaled gases and concentration of second gases in a smaller lung volume due to the high volume uptake of the first gas. Conceptually, the loss of lung volume may be compensated for by decreased expired ventilation or reduction in lung volume as well as increased inspired ventilation. The implication that extra gas is routinely drawn into the lungs to compensate for loss of lung volume, is misleading if compensatory changes are based on decreased expired ventilation.

Cardiac Output:

Large amount of volatile anesthetic from the alveoli is removed by a higher cardiac output and therefore it lowers the partial pressure of the gas in the alveoli. Drug distribution is faster within the body but the partial pressure in the arterial blood is lower. It will take more time for the gas to reach a balance between the alveoli and the brain. Induction time of anaesthetic agents is prolonged by a high cardiac output.

Alveolar Ventilation:

Increased alveolar ventilation, like PI, promotes input of anaesthetics to offset uptake. The net effect is a more rapid rate of increase in the P_A towards the PI and thus induction of anaesthesia. In addition to the increased input, the decreased P_{aco2} produced by hyperventilation of the lungs decreases cerebral blood flow. Conceivably, the impact of increased input on the rate of rise of P_A would be offset by decreased delivery of anaesthetic to the brain. Decreased alveolar ventilation decreases input and slows the establishment of P_A and P_{br} necessary for the induction of anaesthesia. The greater the alveolar ventilation to FRC ratio, the more rapid is the rate of increase in the P_A . In neonates, the ratio is approximately 5:1 compared with only 1.5:1 in adults, reflecting the greater metabolic rate in neonates compared with adults. As a result, the rate of increase of P_A towards the PI and thus the induction of anaesthesia is more rapid in neonates than in adults.

Alveolar to venous partial pressure difference:

The alveolar to venous partial pressure difference is same as, the tissue uptake of the inhaled anesthetic. During the induction phase, a large difference in partial pressure of gas between blood and alveoli is caused by increased uptake of the gas from the alveoli and it causes rapid diffusion of anaesthetic gas from the alveoli into the blood. Perfusion of tissue and

solubility of anaesthetic gas into different tissues determines the uptake of anaesthetic gas from the arterial blood into the tissues. After a equilibrium has been reached between two phases, the partition of gas itself between the two phases is described by the brain or blood coefficient. For instane, Isoflurane has a brain/blood coefficient of 1.6 i.e., the concentration of isoflurane in the brain will be 1.6 times more than isoflurane concentration in the blood, if the gas is in equilibrium. All inhalation anaesthetic agents have high fat or blood partition coefficients i.e., as time goes, most of the gas will attach to a fatty tissue. The concentration of gas in the fatty tissue will rise very slowly by the partial pressure of the gas present in it. In such tissue, the inhalation anaesthetic agents were stored. Thus in obese patients, a delayed awakening occurs during recovery from anaesthesia. The body tissues are divided into four groups based on the level of blood flow and perfusion.

- Muscle group - skin and muscle
- Vessel rich group - heart, liver, brain and kidney
- Vessel poor group - cartilage, bone and connective tissue
- Fat group - minimal flow / large capacity

$$P_A \rightleftharpoons P_a \rightleftharpoons P_{br}$$

The alveolar partial pressure P_A of an inhaled anaesthetic is in equilibrium with the arterial blood P_a and brain P_{br}. As a result, the P_A is an indirect measurement of anaesthetic partial pressure at the brain.

Metabolism and elimination of inhaled anesthetics:

For two reasons the metabolism is important. First, an exposure to carbon dioxide absorbents may be toxic to the liver, kidneys or reproductive organs are due to the intermediary metabolites, end metabolites or the breakdown products. Second, the rate of decrease in the alveolar partial pressure may be influenced by the degree of metabolism at the conclusion of anesthetic.

The amount of inhaled anesthetics metabolized is assessed by the measurement of metabolites or by comparing the total amount of anesthetic in exhaled gases with the amount of anesthetic administered.

Determinants of metabolism:

The magnitude of metabolism of inhaled anesthetics is determined by

- Genetic factors
- Hepatic enzyme activity
- Chemical structure
- Blood concentration

Genetic factors - Drug-metabolizing enzyme activity is the most important determinant that appears in genetic factors. So, when compared to lower animal species humans are the active metabolizers of drugs.

Hepatic enzyme activity – Due to the variety of drugs, the hepatic cytochrome activity P-450 enzymes responsive for metabolism of volatile anesthetics may be increased. Surgical stimulation lasting in patients for 1hour increases the hepatic microsomal enzyme activity due to the technique used. Conversely, surgery lasting more than 4hours results in depressed microsomal enzyme activity.

Chemical structure - In the anaesthetic molecule the most susceptible sites for an oxidative metabolism are the carbon-halogen bond and ether bond.

Blood Concentration – The blood concentration of the anaesthetic influences the fraction of anaesthetic that is metabolized on passing through the liver. For example, during a single passage through the liver, a 1 MAC concentration saturates hepatic enzymes and decreases the fraction of anaesthetic that is removed. Conversely, less than 0.1 MAC undergo extensive metabolism on passage through the liver. As a result, at low blood concentrations conductive to metabolism, a less drug is available to pass through the liver.

ISOFLURANE

R C Terrell and colleagues at Ohio medical products produced isoflurane. Introduced in 1981.

Physical properties:

Isoflurane is a halogenated methyl ethyl ether

It is a clear, nonflammable liquid at room temperature

Has a pungent ethereal odor

Molecular Weight : 184 daltons

Boiling Point : 48.5 °C

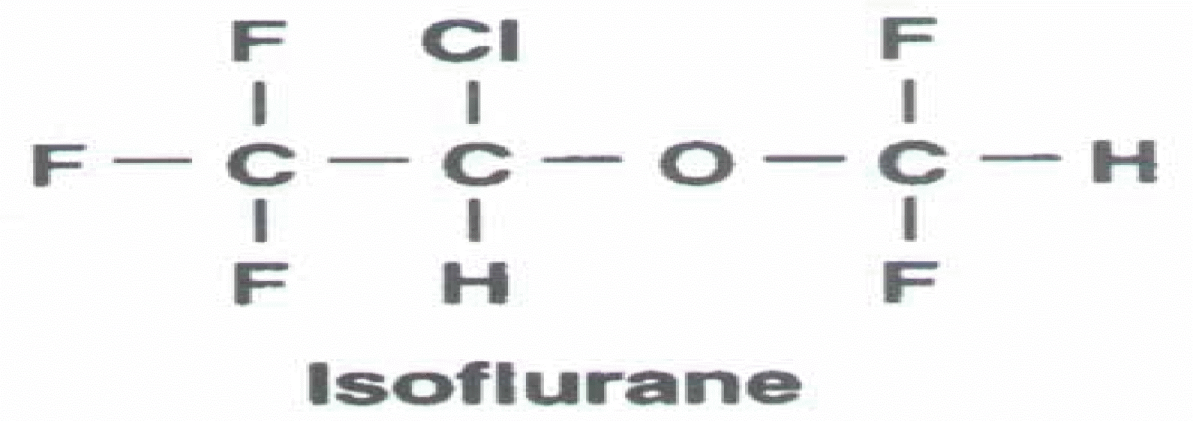
Saturated Vapour pressure (20°C) : 240mmHg

Blood : gas partition coefficient : 1.46

Oil-Gas Partition Coefficient:99

Minimum alveolar concentration : 1.17%
0.5% (70%-N2O/O2)

Chemical name : 2,2,2-trifluoro-1-chloroethyl-difluoromethyl ether



Isoflurane

Pharmacokinetics :

It has different physical and chemical properties though it is a chemical isomer of enflurane. Isoflurane has intermediate solubility in blood and a high potency. It results in rapid induction and recovery from anaesthesia.2,2,2-trifluoroethanol is the starting compound for manufacture of isoflurane. The purification of isoflurane by distillation is complex and expensive. It has extreme physical stability.

Circulation

Isoflurane produces a reduction in blood pressure. It is dose dependant. Vasodilatation and decreased total peripheral resistance caused by isoflurane, especially in muscle and skin is the reason for fall in blood pressure. Isoflurane causes a direct myocardial depression but this is not more evident at normal gas tensions in humans.

Hypercapnia and Sympathetic nervous system stimulation during spontaneous respiration results in an increase in heart rate and cardiac output. The cardiovascular effects of isoflurane are blocked by β-blockers, and it is thought to be as a result of direct stimulation of β-adrenergic receptors.

Myocardial oxygen demand is lowered in proportion to the decrease in myocardial work. Coronary blood flow is unaltered. It suggests the wide

margin of safety for cardiovascular system. It is also a clinical feature of anaesthetic gases like halothane and enflurane.

The dilation of coronary arterioles cause a subendocardial steal syndrome. It results from diversion of blood flow to non ischaemic regions of diseased heart from ischaemic regions. It is seen only in some proportion of severe ischaemic heart disease patients. Cardiac ischaemia caused by isoflurane is only by significant hypotension caused by it. Subendocardial steal syndrome is uncommon.

The arrhythmias caused by isoflurane are uncommon though the heart rate is increased by reflex mechanisms.Ventricular conduction is not affected by isofluane and the excitability of ventricular myocardium is not increased.

Respiratory system:

Isoflurane depresses respiration. It is dose related. It is equivalent to that caused by halothane at 1 MAC. Compared to halothane and enflurane, the normal physiological responses to hypoxia & hypercapnia are lowered to a greater extent.

The tidal volume is decreased in spontaneous respiration,but respiratory rate shows only a little change. There is a similar reduction of pulmonary compliance and functional residual capacity. Isoflurane causes inhibition of hypoxic pulmonary vasoconstriction. This causes a decrease

in efficiency of gas exchange. It is important in case of one lung ventilation. Concentration of isoflurane ≥1 MAC inhibits hypoxic pulmonary vasoconstriction. In case of desaturation during one lung ventilation it is discontinued.

Isoflurane has a pungent ethereal odor. Reflex stimulation of the airway by secretions,laryngospasm and coughing occurs with preanaesthetic doses of isoflurane. Induction by intravenous route is ideal. Bronchodilation is caused by anaesthetic doses of isoflurane like other volatile agents.

NERVOUS SYSTEM

Isoflurane causes cerebral vasodilatation. Cerebral blood flow is raised in spite of the decreased perfusion pressure. Intracranial pressure is raised in proportion to cerebral blood flow.

Cerebrospinal fluid reabsorption is increased and cerebrospinal fluid volume is decreased. It lessens the increase in intracranial pressure. Cerebral vessels are responsive to carbondioxide. Hyperventilation and hypocapnia causes decrease in intracranial pressure.

Electroencephalogram shows some progressive changes with increased depth of anaesthesia,

1 MAC - slow waves with increasing voltage

1.5 MAC - burst suppression

2 MAC - electrical silence

Convulsive activity is not stimulated by isoflurane.

MUSCLE

Isoflurane reduces the response of skeletal muscle caused by sustained stimulation of nerve. The blockade caused by depolarizing and non-depolarizing relaxants is enhanced by isoflurane.

This results from is action on the central nervous system and neuromuscular junction. Peripheral vasodilatation causes raised blood flow to the muscle and it raises the delivery and elimination of these anaesthetic agents from the muscle.It causes smooth muscle relaxation of uterus. It is similar to that caused by enflurane and halothane.

KIDNEY

Isoflurane causes decrease in glomerular filtration rate, blood flow to kidneys and production of urine. It is also dose dependent. The quantity of fluoride ion produced by metabolism of isoflurane is very less and there is no need for precaution for its use in renal disease.

LIVER

The blood flow to liver is decreased and is directly proportional to the perfusion pressure but oxygen supply to liver is not compromised. There is little evidence to prove that isoflurane impairs liver function intraoperatively.

BIOTRANSFORMATION

Isoflurane is metabolized very little in liver about 0.17% and is because of the following factors : the absence of bromine in isoflurane, the presence of the ether bond, the low oil:gas partition coefficient, the F3C-C-O arrangement, increasing C-F bond strength. Greater stability of isoflurane molecule makes in less available to the hepatic metabolism. The major end products of metabolism are trifluoroacetic acid and fluoride ion. The amount of end products released by metabolism is not enough to cause cell damage. But trifluoroacetate reacts with hepatocyte antigen and can form a new protein which induces an antigen antibody reaction causing hepatotoxicity.

HEPATIC EFFECTS OF INHALATIONAL ANAESTHETICS

Hepatic Blood Flow

Isoflurane maintains the total hepatic blood flow and hepatic artery blood flow and increases the portal vein blood flow. Isoflurane is a vasodilator of the hepatic circulation. It has beneficial effects on hepatic oxygen supply. Halothane acts as a vascoconstrictor on the hepatic circulation. Patients receiving 1 MAC isoflurane plus nitrous oxide had an increase in hepatic blood flow and increased hepatic venous oxygen saturation . Halothane with nitrous oxide did not change hepatic blood flow in patients . Halothane administration in healthy patients produces hepatic artery vasoconstriction. Desflurane and Sevoflurane administration maintains hepatic blood flow as same as isoflurane. Postoperative hepatic adverse effects depends on maintenance of oxygen supply of liver relative to its demand during anaesthesia.

Drug Clearance

Volatile anaesthetics interferes with drug clearance from the plasma by decreasing the blood flow to liver or by inhibiting the drug-metabolizing enzymes. Intrinsic clearance by hepatic metabolism of drugs such as propranolol is decreased by 54% to 68% by inhaled anesthetics. Inhibition of hepatic drug- metabolizing enzymes by volatile anaesthetics

is more important than their action on blood flow to liver to decrease the drug clearance.

Liver Function Tests

Enflurane and desflurane administration shows transient increase in alanine aminotransferase levels, but not seen with isoflurane administration in human volunteers. There is transient increase in concentration of alpha glutathione transferase in plasma after administration of isoflurane or desflurane for surgical anaesthesia. In the presence of surgical stimulation, bromsulphalein retention and increases in liver enzymes follow transiently even after the administration of isoflurane, suggesting that changes in hepatic blood flow evoked by painful stimulation can adversely alter hepatic function independent of the volatile anaesthetic.

Hepatotoxicity

Most volatile anesthetics cause postoperative hepatic dysfunction. Halothane is the most common agent causing liver dysfunction among them. The incidence of centrilobular necrosis is more with halothane, in the study of various anaesthetic agents in hypoxic rat model ,that includes enzyme induction. The principle mechanism responsible for liver dysfunction following anaesthesia is insufficient hepatic oxygenation.

Adequate oxygenation of hepatocyte is interfered by agents affecting alveolar ventilation or decreasing hepatic blood flow. Enzyme induction may create a increase in oxygen demand and make patients more vulnerable to decreased hepatic oxygen supply caused by action of anaesthetics on oxygen delivery of liver. Preexisting liver disease may be associated with marginal hepatocyte oxygenation, which would be further jeopardized by the depressant effects of anaesthetics on hepatic blood flow and/or arterial oxygenation. Indeed, liver transaminase enzymes are increased more in cirrhotic than noncirrhotic animals exposed to halothane. Hypothermia protects the liver from drug induced ischaemic injury by decreasing the hepatic oxygen demand.

Halothane

Hepatotoxicity produced by halothane is of two types in susceptible patients. First type is a mild, self-limiting postoperative hepatotoxicity. It comprises of symptoms like nausea, hyperthermia and lethargy. Elevation in plasma concentrations of liver transaminase enzymes is also seen. It is seen in 20% of adult patients. The second type of hepatotoxicity may lead to lethal hepatic necrosis and liver failure causing death. It is rarer than the first type of hepatotoxicity. Adults are more susceptible to this type of hepatotoxicity than children. The changes in hepatic blood flow and oxygenation caused by halothane is most likely the reason for more

common type of hepatotoxicity which is a self-limited form of hepatic dysfunction. Immune-mediated hepatotoxicity is the proposed mechanism behind the rare life-threatening hepatic dysfunction known as halothane hepatitis .

Halothane Hepatitis

Immune mediated reaction in halothane hepatitis has clinical manifestations like fever, rash, eosinophilia, arthralgia and previous exposure to halothane. Risk factors that are related to halothane hepatitis are female gender, middle age, obesity and multiple exposures to halothane. Acute hepatitis is the predominant histologic feature. Circulating immunoglobulin G antibodies in most of the patients with halothane hepatitis is the proof of an immune-mediated mechanism . The trifluroacetyl halide metabolite produced by metabolism of halothane reacts with the liver microsomal proteins present on the surface of hepatocytes.The metabolite is a reactive oxidative species that causes covalent modification of liver antigens to form neoantigens. This acetylation of liver proteins changes these proteins from self to nonself. Antibodies are formed against these new proteins. Antigen-antibody interaction is responsible for hepatic injury in halothane hepatitis. Genetic factors are suspected to be associated with halothane hepatitis as per case

reports of hepatitis in closely related relatives. Indeed in human beings the halothane metabolism appears to be under the influence of genetic factors.

Reductive metabolism is not the primary mechanism in the development of halothane hepatitis. Enflurane and isoflurane both produce centrilobular necrosis in the hypoxic rat model, but neither of them undergo reductive metabolism. Metabolites produced by reductive metabolism of halothane do not themselves directly produce hepatotoxicity. Fasting enhances hepatotoxicity caused by volatile anaesthetics but no role in alteration of metabolism .

MECHANISM OF HEPATOTOXICITY BY ISOFLURANE

The postoperative hepatic dysfunction which is associated with the volatile anaesthetics reflects the alterations in hepatic oxygen delivery which is related to demand that results in inadequate hepatocyte oxygenation. A mechanism same as that of that of halothane is seen with isoflurane .They are oxidative metabolism by liver enzymes (cytochrome P-450 enzymes), which forms acetylated liver protein adducts. Acetylated liver proteins which are capable of initiating an antigen antibody reaction can occur after exposure to isoflurane. In hepatitis associated with isoflurane trifluroacetyl modified new proteins have been described as a possible mechanism for hepatotoxicity. This increases the chance of isoflurane to produce hepatotoxicity similar to halothane by similar

mechanism. It occurs at a lower incidence because the magnitude of hepatocyte injury is directly proportional to the amount of anaesthetic metabolized by liver. Considering the degree of volatile anaesthetic metabolism , it is predictable that the incidence of hepatitis would be more with halothane, intermediate with use of enflurane and rare but can occur with isoflurane. Desflurane is very safe as it have the lowest level of adduct formation and have least chance for immune-mediated hepatitis because it is metabolized even less than isoflurane. Massive hepatotoxicity can be precipitated by very less amount of adduct, especially if the patient was sensitized against trifluroacetyl proteins during previous surgery. Hepatotoxicity after desflurane anesthesia has been described in a patient who might have sensitized by exposure to halothane previously. Fulminant hepatic failure has been absorbed in a patient 22 years following exposure to enflurane. It was accompanied by high plasma concentrations of CYP2A6 autoantibodies. Halothane is capable of sensitizing the patients against newly altered hepatocyte antigen formed by other fluorinated volatile anaesthetic agents.

Rare patients who have been sensitized due to a previous exposure to halothane can be detected by enzyme-linked immunosorbent assay by measuring antibodies evoked by acetylation. They are at increased risk for subsequent exposure to other fluorinated volatile anesthetics. The

overall risk associated with anaesthesia is more than the risk of fulminant massive hepatic failure caused by exposure to enflurane, isoflurane or desflurane following a previous exposure to halothane.

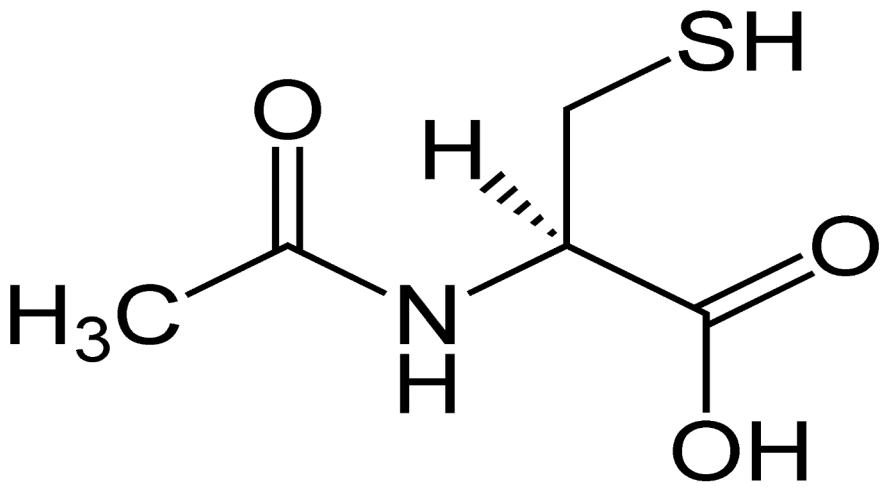
Operating room personnel exposed to trace concentrations of volatile anaesthetic gases might have stimulation of antibody production. Measurement of plasma autoantibody concentrations in paediatric anaesthesiologists showed increased levels compared with general anaesthesiologists and controls. It is presumed that paediatric anaesthesiologists are at increased risk for exposure to trace concentrations of volatile anaesthetic gases because of the frequent use of nonrebreathing anaesthesia delivery systems and use of uncuffed endotracheal tubes in paediatric patients. Though high antibody levels are seen in paediatric anaesthesiologists, these antibodies may be insufficient to cause damage to normal hepatocytes.

Sevoflurane

The chemical structure of sevoflurane defines that it cannot get metabolized to an acetyl halide like other fluorinated volatile anaesthetic agents. Metabolism of sevoflurane does not cause the formation of trifluoroacetylated liver proteins. It would not stimulate the production of antibodies against trifluoroacetylated liver protein like other volatile gases like halothane, enflurane and isoflurane.

N ACETYL CYSTEINE

Acetylcysteine is the *N*-acetyl derivative of L-cysteine. It is a precursor in the production of the glutathione in the body which is a well known antioxidant.The sulfhydryl group in it is responsible for its antioxidant effects. It helps to decrease free radical damage.



Acetylcysteine is a cysteine derived compound with a acetyl group that is combined to the nitrogen atom. This compound is marketed as a dietary supplement for its antioxidant function and liver protecting effects. It is used as a cough medication because it disintegrates disulfide bonds in mucus and thick mucus is liquefied. Its action of breaking disulfide bonds is used in conditions like cystic and pulmonary fibrosis to thin out secretions.

World Health Organization's list of Essential medicines added acetyl cysteine in the most important list of medication needed in a basic health system.

MECHANISM OF ACTION

Acetylcysteine is a prodrug of L-cysteine. L-cysteine is a precursor for glutathione which is an antioxidant. Acetylcysteine fills up the depleted glutathione stores in the body. L-cysteine also serves as a precursor to cystine. It is a essential substrate for the cystine-glutamate antiporter present on astrocytes .It raises the amount of glutamate released into the extracellular space. This glutamate has its effect on $mGluR_{2/3}$ receptors and at higher concentrations of acetylcysteine it acts on $mGluR_5$. The NMDA receptor is modulated by glutathione by its action at the redox site. Acetylcysteine also inhibits NF-κB and alters cytokine synthesis.This is responsible for its anti inflammatory activity. In certain brain areas it facilitates release of dopamine.

GLUTATHIONE

Glutathione (GSH) is a most vital antioxidant in all living things(plants, animals, fungi and some bacteria) They prevent the free radical damage produced by reactive oxygen species like peroxides. Glutathione consists of three amino acids. It has a gamma peptide bond in between the carboxyl group of the glutamate side-chain and the amine group of cysteine. Glutathione donates electron and reduces disulfide bonds created within proteins in cytoplasm. During the process, glutathione is changed to its oxidized form which is glutathione disulfide (GSSG). Glutathione

reductase reduces glutathione back to its original form by using NADPH which is an electron donor. The ratio obtained by reduced glutathione to oxidized glutathione inside the cells is used as a predictor of toxic cell damage.

DOSAGE FORMS :

Acetyl cysteine is available in a variety of formulations for various disorders :

Inhalation form (Mucomyst, Mucosil) – used for mucolytic therapy and taken to prevent renal damage(nephroprotective effect)

Intravenous injection (Assist, Acetadote) – treatment of paracetamol poisoning

Oral solution

Effervescent Tablets (200 mg)

Ocular solution - for mucolytic therapy

Sachet (600 mg) and PharmaNAC Effervescent Tablets (900 mg)

USES OF ACETYL CYSTEINE

PARACETOMOL POISONING: Both intravenous and oral drug formulations of acetylcysteine are being widely prescribed for the treatment of paracetamol poisoning .A minor end product of paracetomol metabolism called N-acetyl-p-benzoquinone imine gets accumulated inside the body in paracetomol poisoning. This toxic compound is conjugated with glutathione in liver and made non toxic. But glutathione reserves in liver are not sufficient. This metabolite reacts freely with hepatic enzymes causes hepatocyte injury. This may cause acute liver failure because of massive liver damage and death.

Acetylcysteine refills the depleted glutathione stores in the hepatic system and accentuates the non-toxic metabolism of paracetomol. These effects of acetyl cysteine helps to protect liver from NAPQI toxicity. Acetyl cysteine is very efficacious within 8–10 hours after overdose in preventing liver damage.

Mucolytic therapy: Acetylcysteine is used as an adjuvant for the treatment of respiratory diseases with excessive thick mucus production like emphysema, bronchitis, cystic fibrosis, tuberculosis , bronchiectasis, amyloidosis, pneumonia, COPD, and pulmonary fibrosis .It acts like a mucolytic agent. Its mucus dissolving property is used in tracheostomy care. Oral acetylcysteine modifies inflammation in cystic

fibrosis at high doses and has the ability to modulate the redox and inflammatory imbalances in cystic fibrosis. Acetylcysteine breaks the disulfide bonds between proteins present in the thick mucus and acts to reduce the viscosity of mucus.

OTHER USES :

Preventing radiocontrast-induced nephropathy

Cyclophosphamide-induced hemorrhagic cystitis

Petroff's method in microbiology for liquefying and decontaminating the infected sputum for recovery of mycobacterium from it.

It has antiviral activity against the influenza A viruses.

Preventing disease progression of Interstitial lung disease

Treatmentfor schizophrenia, bipolardisorder,trichotillomania, skin picking, autism, obsessive-compulsive disorder, drug and gambling addiction. Preventing disease progression of Alzheimer disease.

ADVERSE EFFECTS

The most common adverse effects seen with intravenous injection of acetylcysteine are rash, pruritis and urticaria. Anaphylactoid reaction includes rash, hypotension, wheezing, and shortness of breath. Inhalational form of acetylcysteine can cause adverse effects such as nausea, vomiting, hyperthermia, rhinorrhea, lethargy, clamminess, stomatitis, chest tightness

and bronchospasm. Oral forms of acetylcysteine can cause side effects such as nausea, vomiting, rashes and fever. Antioxidants have the ability to prevent toxic cell damage caused due to reactive oxygen species. Antioxidants supplemented by food industry for their ability to prevent cancer. Diet supplementation with the antioxidants like N-acetylcysteine and vitamin E greatly raised the progression of tumor in mouse models of B-RAF and K-RAS oncogenes induced lung cancer. Sequencing of RNA showed that N acetyl cysteine and vitamin E are structurally not related but have a chance to cause coordinated alterations in tumor transcriptome profiles. It was associated with decreased expression of endogenous antioxidant genes. They may enhance the progression of early cancers or precancerous condition in high-risk populations such as smokers and patients with COPD who receive NAC to dissolve thick mucus. In a mouse model very high doses of acetylcysteine have reported to cause damage to the heart and lungs. A end product of acetyl cysteine metabolism, S-nitroso-N-acetylcysteine (SNOAC) raises pressure in the pulmonary vasculature and right ventricle of the heart resulting in pulmonary artery hypertension in mice administered with acetylcysteine. It was same as the effect caused by chronic hypoxia.

The results of these mouse studies have not yet been investigated. The dose used in the mouse models was greatly higher than that used in

human beings which was about 20 grams per day. N-acetylcysteine protected liver from toxic damage when taken before consumption of alcohol, but when taken lately about 4 hours after consumption of alcohol it worsened the damage to liver depending on the dose taken.

RESEARCH

- There is some evidence about the usefulness of acetylcysteine in traumatic brain injury.
- It has been suggested that acetylcysteine increase the levels of glutathione and allows rapid breakdown of salicylates in patients suffering from Sampter's traid. There is no evidence of its benefit.
- It has been found to be beneficial in women with polycystic ovary syndrome to reduce insulin resistance and can treat infertility.
- Some minor studies have suggested that acetylcysteine is useful in patients suffering with blepharitis. In Sjogren's syndrome it was found to have capacity to decrease ocular soreness.
- In an open trial in 4 patients it has been found to be beneficial in the management of Unverricht-Lundborg disease . A great decrease in myoclonus and modification of somatosensory evoked potentials to its normal level with administration of acetylcysteine has been found.

- The action of acetylcysteine combined with glucocorticoids for sufferers of severe alcoholic hepatitis was analysed and found that the group treated with acetylcysteine combined with prednisolone showed significant reduction in mortality rate at one month compared to the group managed with prednisolone alone. However, the improvement was insignificant at 3 months or 6 months. Increased 6-month survival was associated with factors like younger age, short prothrombin time, lower levels of bilirubin and decrease in bilirubin on day 14, all ($P<0.001$).In the combination group at 6 months mortality due to hepatorenal syndrome occurred less frequently and less frequent infection is seen group treated with acetylcysteine combined with prednisolone. The primary outcome after analyzing the six month survival was not improved in conclusion.

LIVER METABOLISM

The liver is located in the right hypochondrial region of the abdomen. The functions of the liver are: stores the glycogen, that is made from glucose, helps in processing of proteins and fats from digested food, synthesize proteins that are needed for clotting factors; process drugs and helps to remove toxins and poisons from the circulation. The liver produces bile, which is like a greenish-yellow in colour that consists of bile pigments, bile acids and certain waste products such as bilirubin. The hepatocytes secretes bile into bile ducts present within the liver. The bile leads to the common bile duct when it flows down the ducts into larger ducts. The gallbladder acts like a bile reservoir that continues with the common bile duct. When gallbladder contracts bile is squeezed back into the common bile duct and pass down into the duodenum. Duodenum is the first part of the gut after the stomach which helps to digest fats.

Enzymes which are located in the endoplasmic reticulum of hepatocytes helps to protect against an accumulation of lipid-soluble exogenous and endogenous substances. This is done by changing them into water-soluble end products which can be easily excreted out by the kidney.

The liver is the principal site of drug metabolism. Eventhough drug metabolism in liver inactivates the parent drug, the drug metabolites sometimes have role in pharmacokinetics. An inactive compound or a

weakly active compound that can be converted into a active metabolite is called a prodrug.

Drugs can undergo metabolism by reduction, oxidation, hydration, hydrolysis condensation or conjugation. The main aim was to convert the drug to a compound which is easier to excrete whatever process is done. The enzymes that are taking place in metabolism are found in many other tissues but they are highly concentrated in the hepatic system. The rate at which drug metabolism takes place varies between patients. In certain patients drug metabolism takes place very rapidly so that therapeutically effective drug concentrations are not obtained in blood and tissues. While in other patients, drug metabolism occurs at a very slow rate and usual therapeutic doses cause toxic effects. Genetic factors, coexisting disorders which particularly includes advanced heart failure and chronic liver disorders, and drug interactions that involve inhibition or induction of metabolism influences the individual drug metabolism rates.

Metabolism takes place in 2 phases for many drugs:

Phase I reactions: Phase I enzymes include cytochrome P-450 enzymes, non-cytochrome P-450 enzymes and flavin containing monooxygenase enzymes. Cytochrome P-450 enzymes are membrane bound heme proteins.

Many enzymes act to introduce two groups such as reactive groups and polar groups into their substrates. The important modification is that hydroxylation is catalyzed by the cytochrome P-450, which is a dependent mixed-function oxidase system. These enzyme complexes has its action by introducing an atom of oxygen into non activated hydrocarbons. It results either in the introduction of hydroxyl groups or N-, O- and S-dealkylation of substrates. The P-450 oxidases acts by reducing the oxygen bound to cytochrome and the production of a highly-reactive oxyferryl species. The phase I reactions are known as non synthetic.

Cytochrome P-450:

The most vital enzyme complex of phase I reaction is cytochrome P-450 (CYP450).It is a microsomal superfamily of isoenzymes which is involved in the oxidation of many drugs. A flavoprotein, NADPH–CYP450 reductase transfers electrons from NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) to CYP450. Many other drugs induce or inhibit CYP450 enzymes which results in drug interactions. Through this mechanism a drug may enhance the toxicity or reduce the therapeutic effect of another drug.

Liver parenchyma and blood flow are decreased with increasing age. Thus with increasing age the metabolism taking place through cytochrome P-450 enzyme is reduced. Drugs which are metabolized through

cytochrome P-450 enzyme reach elevated levels in old age. The half-life of the drugs are also prolonged in the elderly. The hepatic microsomal enzyme activity is not well developed in neonates as in adult age group. Hence, in neonates drug metabolism is difficult and they are prone for drug toxicity.

Phase II reactions:

Phase II enzymes are glucuronosyltransferase, N-acetyl transferase, glutathione-S-transferase and sulfotransferase.

Conjugation with an endogenous substance takes place in phase II reactions. The examples for endogenous substance are glucuronic acid, sulfate, glycine,glutathione. The phase II reactions are also known as synthetic reactions. Metabolites formed in phase II reactions are more polar than those formed in non synthetic reactions and so they are easily excreted in the urine and bile.

Conjugation:

The most common phase II reaction is glucuronide conjugation or glucuronidation. The uridine diphosphate glucunosyl transferase enzyme catalyzes the addition of glucuronic acid to variety of exogenous and endogenous compounds. After conjugation glucuronides are secreted

through bile and excreted in urine. By this process, the drugs are made more soluble. They are excreted easily in urine by kidneys. Beta-Glucuronidase in intestine hydrolyzes the glucuronides and convert them to their present compounds which is reabsorbed from the intestine and transferred again to liver to undergo reconjugation. This process is called entero hepatic circulation. Glycine and glutamate conjugation also produces conjugates which are eliminated by kidneys through urine. But, they are not secreted through bile like glucuronide conjugates. Glucuronidation is not affected by age. However, in case of neonates, the process of glucuronidation is slow and it results in serious effects. Acetylation by N-acetyl transferase is used for inactivation of heterocyclic aromatic compounds. Sulfate esters are water soluble and are easily excreted in urine.

Rate of metabolism:

The rate of metabolism of every drug in any given pathway of metabolism has a capacity limitation. Usually a minor fraction of the active sites of metabolizing enzyme are occupied at therapeutic concentrations of most drugs. It increases the metabolism rate with drug concentration and that case is called first-order elimination i.e., the drug has a specific half-life). For instance, if 400 mg of a drug is present in the body at time zero, at the end of metabolism, 200 mg may be present at 1

hour and 100 mg at 2 hours. Zero order kinetics occurs when the active sites of the metabolizing enzyme are saturated. Drug metabolism happens at a maximum rate but rate of metabolism cannot be increased beyond this point. In this case, if 400 mg is present in the body at time zero, at the end of metabolism, 350 mg may be present at 1 hour and 300 mg at 2 hour (showing a maximal clearance of 50 mg/h and no specific half-life).Metabolism shifts from first-order to zero-order kinetics with the increase in drug concentration.

Hepatic Clearance:

Hepatic Clearance of a drug depends on blood flow to the liver and hepatic extraction ratio. Hepatic blood flow determines the clearance of a drug if hepatic extraction ratio is high. Enzyme activity has a minimal influence. This is called as perfusion dependant elimination. Low hepatic extraction ratio denotes that only a minor fraction of drug is eliminated per unit of time. Excess drug is available for liver metabolism. A decrease in protein binding or increased enzyme activity helps in hepatic clearance of the drug with low hepatic extraction ratio. Changes in hepatic blood flow will have minimal influence on clearance of the drug by liver. This is known as capacity dependent elimination.

LIVER FUNCTION TESTS

Various functions are performed by the liver. It produces certain substances that pass into bile and bloodstream. The blood level of these chemicals is altered by various liver disorders. Blood sample is measured for some of these chemicals.

A group of blood tests called Liver function tests (LFTs) detects the inflammation and identifies the damage in the liver. The functional capability of liver can be assessed by liver function tests. Liver enzyme testing consists of alanine aminotransferase, aspartate aminotransferase , alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase and true liver function tests include prothrombin time, INR, albumin, and bilirubin.

USES OF LIVER FUNCTION TESTS

- It helps to diagnose the type of jaundice caused by liver dysfunction. Based on the type of enzyme elevated the liver function test helps to differentiate the reason for increased bilirubin.
- To assess the severity and prognosis of liver disorders.
- To assess whether a drug has hepatotoxic potential before starting the patient on medication.

- To screen high risk patients like alcoholics and hepatitis viral carriers for any serious liver damage.

Bilirubin.

Bilirubin is produced from haemoglobin. When the red blood cells disintegrate hemoglobin is released.Bilirubin is taken by hepatocytes and sugar molecules are attached to it. Bilirubin has an open chain of four pyrrole-like rings. In heme, these four rings are connected into a porphyrin ring.

Bilirubin can be conjugated with a molecule of glucuronic acid which makes it water soluble. This process is a type of glucuronidation. Bilirubin is same as phycobilin present in algae to entrap light energy, and similar to phytochrome pigment present in plants to sense light . They consists of open chain of four pyrrolic rings.

Biliverdin is a product of heme catabolism. It is a green tetrapyrrolic bile pigment. It is reduced by biliverdin reductase to bilirubin. Oxidation of bilirubin produces back biliverdin. This shows that bilirubin acts as a potent physiological antioxidant.

Conjugated bilirubin

In the hepatocytes, bilirubin is conjugated with glucuronic acid with the help of the enzyme glucuronyltransferase, making it water soluble. The conjugated form is commonly called as "direct" bilirubin. Most of the direct bilirubin is secreted through the bile into the duodenum. Most bile acid is reabsorbed in the terminal ileum(enterohepatic circulation) but conjugated bilirubin or direct bilirubin is not absorbed and instead passes into the colon.

Colonic bacteria deconjugates and metabolizes the bilirubin to colourless urobilinogen. Urobilinogen is oxidized to generate urobilin and stercobilin. Brown color of stool is due to stercobilin . A small amount of urobilinogen is reabsorbed from intestine into the enterohepatic circulation. It is again excreted through bile and some of this is taken by the kidneys and excreted in urine.

A high blood level of direct bilirubin is seen in various diseases of hepatobiliary system. It is high specially in conditions causing obstruction to the bile flow. For instance, by a gallstone obstructing the common bile duct, or by a tumour in the pancreas. It can also be increased in conditions like hepatitis, liver injury or chronic alcohol abuse.

Unconjugated bilirubin

Erythrocytes produced in the bone marrow are disintegrated in the spleen when they get old or damaged. This releases hemoglobin which is then split into heme and globin. Globin is converted to amino acids. The heme is converted into unconjugated bilirubin in the reticuloendothelial cells of the spleen. This unconjugated bilirubin is insoluble in water, because of its intramolecular hydrogen bonding. It is then attached to albumin and transported to the liver.

The measurement of direct bilirubin is based on its reaction with diazosulfanilic acid to produce azobilirubin. However, unconjugated bilirubin also reacts slowly with diazosulfanilic acid, so that the measured indirect bilirubin is an underestimate of the true unconjugated concentration.

A raised level of indirect bilirubin is seen when there is more breakdown of erythrocytes as in haemolytic anaemia.

PROTHROMBIN TIME

The vitamin K–dependent clotting factors (II, VII, IX, and X)are generated in the liver, along with factors V, XI, XII, and XIII and fibrinogen, which are not dependent on vitamin K for synthesis. If the fat-soluble vitamin K is deficient, as in obstructive jaundice, or if it is antagonized by one of the coumarin anticoagulants, the production of

clotting factors takes place at the normal rate, but they will be deficient in g-carboxylglutamic acid residues, which are attached in a post-translational event with the help of vitamin K. The half-lives of the clotting factors are comparively short and defects in coagulation happens rapidly in acute hepatotoxicity. The actual level of coagulation factors in the plasma denotes a balance between production and elimination, and because the liver also produces inhibitors of both coagulation and fibrinolysis, a crisis of low production and increased breakdown may occur in acute liver damage. Thus, prolongation of prothrombin time caused because of deficiency of factors II, V, VII, and X was noted in parenchymal liver disease. When included in liver function test, the prothrombin time has shown great value for predicting the prognosis of patients suffering from acute hepatic failure caused by ingestion of hepatotoxin and also in patients with liver disease who are undergoing surgery.

The prothrombin time is most commonly measured using blood plasma. Blood is taken into a test tube having liquid sodium citrate, which binds calcium in the blood sample and functions as a anticoagulant. The blood is mixed and then centrifuged to split RBCs from plasma.

The sample is analyzed by a laboratory technician with a help of an automated instrument at 37 °C (as a nominal approximation of normal human body temperature), which takes a sample of the plasma.The

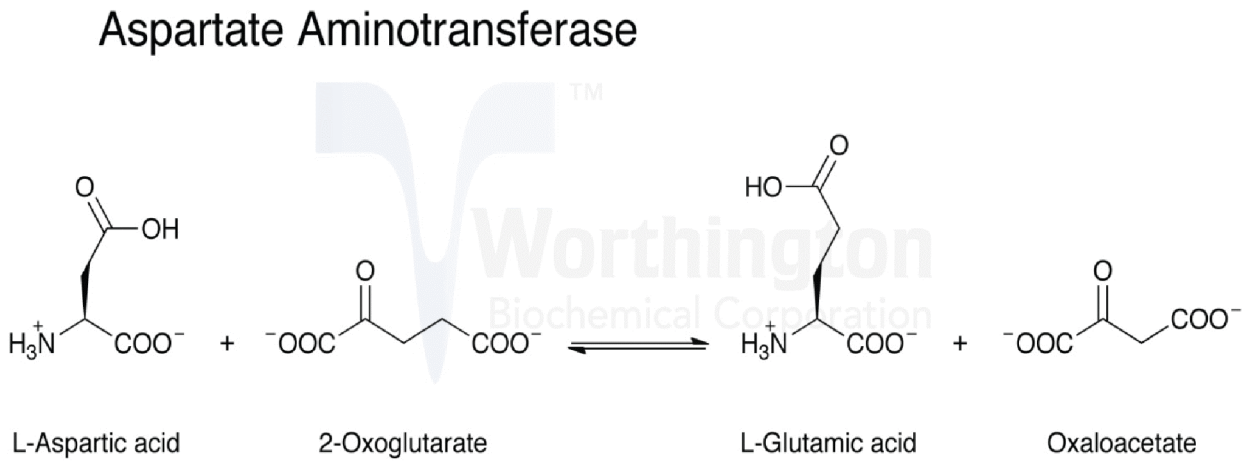
action of citrate is reversed by adding high amount of calcium and makes the blood to clot again. For the purpose of exact measurement, the proportion of blood to citrate wants to be standardized.Accurate measurement is difficult if the tube contains small amount of sample and proportionately high amount of citrate. If the sample tube was underfilled or overfilled with blood than the mentioned amount it is impossible to get the standardized dilution of 1 part anticoagulant to 9 parts whole blood.Sodium citrate tube is the ideal sample for prothrombin time test .

Tissue factor (also known as factor III) is added to the sample, and the time the blood sample takes to clot is analyzed by optical method. Certain labs use a mechanical measurement, which eliminates error due to interferences from lipemic and icteric blood samples. The prothrombin ratio is calculated by dividing the prothrombin time for a patient by prothrombin time for control plasma.

ASPARTATE TRANSAMINASE

Aspartate transaminase (**AST**) or **aspartate aminotransferase**, also known as **serum glutamic oxaloacetic transaminase** (**SGOT**), is a pyridoxal phosphate (PLP)-dependent transaminase enzyme . AST catalyzes the reversible transfer of an α-amino group between aspartate and glutamate and, as such, is an important enzyme in amino acid metabolism.

AST is found in the liver, heart, skeletal muscle, kidneys, brain, and red blood cells, and it is commonly measured clinically as a marker for liver health. Aspartate transaminase catalyzes the interconversion of aspartate and α-ketoglutarate to oxaloacetate and glutamate.



Aspartate (Asp) + α-ketoglutarate ↔ oxaloacetate + glutamate (Glu)

As a prototypical transaminase, AST relies on PLP (Vitamin B6) as a cofactor to transfer the amino group from aspartate or glutamate to the corresponding ketoacid. In the process, the cofactor shuttles between PLP and the pyridoxamine phosphate (PMP) form. The amino group transfer catalyzed by this enzyme is crucial in both amino acid degradation and biosynthesis. In amino acid degradation, following the conversion of α-ketoglutarate to glutamate, glutamate subsequently undergoes oxidative deamination to form ammonium ions, which are excreted as urea. In the

reverse reaction, aspartate may be synthesized from oxaloacetate, which is a key intermediate in the citric acid cycle.

Two isoenzymes are present in a wide variety of eukaryotes. In humans:

- The cytosolic isoenzyme in red blood cells and heart.
- The mitochondrial isoenzyme is present predominantly in liver.

These isoenzymes are thought to have evolved from a common ancestral AST via gene duplication, and they share a sequence homology of approximately 45%.

AST has also been found in a number of microorganisms, including *E. coli*, *H. mediterranei* and *T. thermophilus*. In *E. coli*, the enzyme is encoded by the *aspC* gene and has also been shown to exhibit the activity of an aromatic-amino-acid transaminase

Aspartate transaminase, as with all transaminases, operates via dual substrate recognition; that is, it is able to recognize and selectively bind two amino acids (Aspartate and Glutamate) with different side-chains. In either case, the transaminase reaction consists of two similar half-reactions that constitute what is referred to as a ping-pong mechanism. In the first half-reaction, amino acid 1 (e.g., L-Asp) reacts with the enzyme-PLP complex to generate ketoacid 1 (oxaloacetate) and the modified enzyme-PMP. In the second half-reaction, ketoacid 2 (α-ketoglutarate) reacts with

enzyme-PMP to produce amino acid 2 (L-Glu), regenerating the original enzyme-PLP in the process. Formation of a racemic product (D-Glu) is very rare.

AST is similar to alanine transaminase (ALT) in that both enzymes are associated with liver parenchymal cells. The difference is that ALT is found predominantly in the liver, with clinically negligible quantities found in the kidneys, heart, and skeletal muscle, while AST is found in the liver, heart (cardiac muscle), skeletal muscle, kidneys, brain, and red blood cells. As a result, ALT is a more specific indicator of liver inflammation than AST, as AST may be elevated also in diseases affecting other organs, such as myocardial infarction,acute pancreatitis, acute hemolytic anemia, severe burns, acute renal disease, musculoskeletal diseases, and trauma.

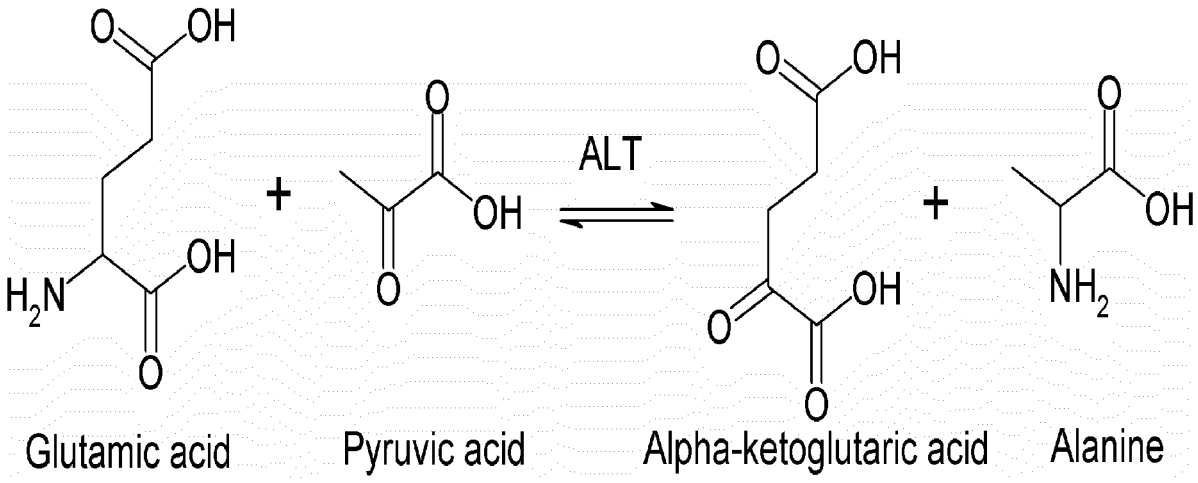
AST was defined as a biochemical marker for the diagnosis of acute myocardial infarction in 1954. However, the use of AST for such a diagnosis is now redundant and has been superseded by the cardiac troponins. AST is commonly measured clinically as a part of diagnostic liver function tests, to determine liver health. Laboratory tests should always be interpreted using the reference range from the laboratory that performed the test. Normal levels of AST are:

Male : 8 to 40 IU/L Female : 6 to 34 IU/L

ALANINE AMINOTRANSFERASE

Alanine transaminase (**ALT**) is a transaminase enzyme. It is also called **alanine aminotransferase** (**ALAT**) and was formerly called serum glutamate-pyruvate transaminase (SGPT) or serum glutamic-pyruvic transaminase (SGPT).

ALT is found in plasma and in various bodily tissues, but is predominantly found in the liver. It catalyzes the two parts of the alanine cycle. It catalyzes the transfer of an amino group from L-alanine to α-ketoglutarate, the products of this reversible transamination reaction being pyruvate and L-glutamate.



Alanine transaminase needs the coenzyme pyridoxal phosphate, which is changed into pyridoxamine during the first phase of the reaction at which an amino acid is changed into a keto acid.

It is frequently measured for the determination of severity liver injury and to evaluate normal functioning of liver. When it is measured it is represented in terms of international units/liter (IU/L). For experimental studies,alanine transaminase levels of 10-40 IU/L is taken as the standard reference range. Alanine transaminase shows a diurnal variation.

The ratio of ALT to AST (aspartate transaminase) has some clinical significance.

Normal level of ALT is 7 to 56 IU per litre of serum.

Significantly raised levels of alanine transaminase commonly suggests the presence of liver disorder like viral hepatitis, liver injury, bile duct problems, infectious mononucleosis, or diabetes, congestive heart failure, myopathy and hence ALT is helpful in diagnostic evaluation for liver problems. Elevated ALT is also seen in choline deficiency in diet. Raised levels of ALT does not always point to the presence of a medical disorder. Fluctuation of ALT levels is normal over the course of the day, and they can also increase in response to strenuous physical exercise.

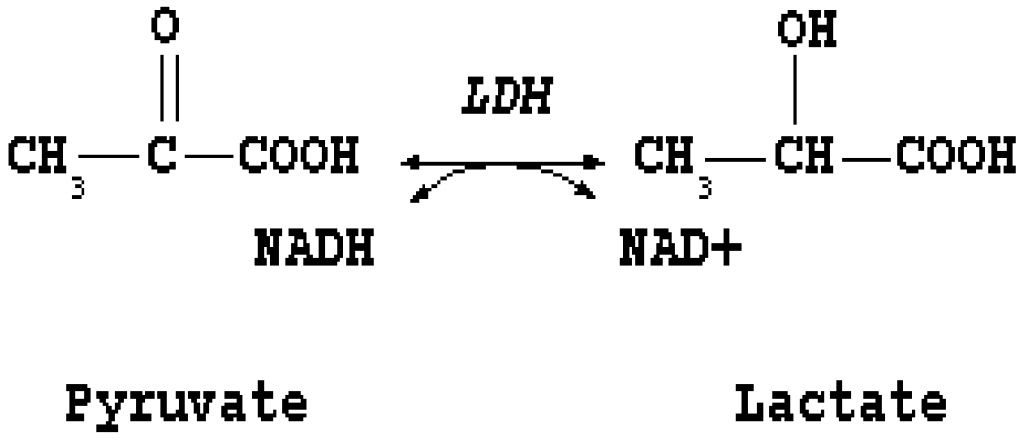
When there is raised level of ALT in the blood, the probable diagnosis can be narrowed down by analyzing the other enzymes. For instance,raised level of ALT due to hepatocellular injury can be differentiated from disease of bile duct by measuring levels of alkaline phosphatase. Elevated levels of ALT in myopathy can confirmed by

measuring creatine kinase . Many drugs may elevate ALT levels, including Zileuton, omega-3-acid ethyl esters, anti-inflammatory drugs, antibiotics, cholesterol medications, some antipsychotics such as risperidone, and anticonvulsants.

LACTATE DEHYDROGENASE

An enzyme found in plants, animals and prokaryotes is a **lactate dehydrogenase (LD**). Lactate dehydrogenase involves the medical significance because, it is found mainly in body tissues, such as heart muscle and blood cells. During tissue damage it is released and is a marker of injuries and diseases.

An enzyme that transfers a hydride from one molecule to another molecule is called a dehydrogenase. In lactate dehydrogenase, the conversion of pyruvate to lactate is catalyzed and also it converts NADH to NAD^+ and in reverse.



Lactate dehydrogenase consists of four different enzyme classes. Each one acts on either D-lactate dehydrogenase or L-lactate dehydrogenase. Among the four enzyme classes, two are cytochrome C dependent enzymes and other two are NAD(P)-dependent enzymes.

The interconversion of pyruvate and the interconversion of NADH and NAD^+ are catalyzed by lactate dehydrogenase. It converts the final product of glycolysis i.e., pyruvate to lactate when oxygen is not present. During the Cori cycle in the liver it performs the reverse reaction. The enzyme exhibits feedback inhibition at high concentrations of lactate, and it decreases the rate of conversion of pyruvate to lactate. The dehydrogenation of 2-Hydroxybutyrate is catalyzed, but it is a worse substrate than lactate and there is no activity with beta-hydroxybutyrate.

Functional lactate dehydrogenase are homo or hetero tetramers consisting of M and H subunits.

- LD-1 : Heart and in RBC (red blood cells)
- LD-2 : Reticuloendothelial system
- LD-3 : Lungs
- LD-4 : Kidneys, placenta, and pancreas
- LD-5 : Liver and striated muscle

There are five isoenzymes and each one contains four subunits. H_4 is the main isoenzyme found in heart muscle, consisting of four heart H subunits. Skeletal muscle and liver is the main isoenzymes called M_4, which has four muscle M subunits. Basically LD-2 is the predominant form in the serum.

SUMMARY OF PRIOR PUBLICATIONS

1. Beyaz et al, The study conducted in 41 ASA I & II patients patients comparing the antioxidant effects of isoflurane and N-acetylcysteine(NAC) on the liver function showed that the liver functions are well preserved with administration of N-acetyl cysteine during anaesthesia with isoflurane. Patients in the study were posted for laparoscopic gynecological surgeries. They were classified into two groups. Placebo group and NAC group. Blood samples were collected preoperatively and at 1st and 24hrs postoperatively and tested for glutathione S-transferase (GST) levels, malondialdehyde (MDA) levels, aspartate amino transferase (AST) levels, alanine amino transferase (ALT) levels, lactate dehydrogenase (LDH) levels, gamma glutamyltranspeptidase (GGT) levels and coagulation profile which includes prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR).There were no statistically significant difference between the two groups in levels of ALT,AST GGT and LDH at preoperative, postoperative 1st hour and postoperative 24th hour ($P>0.05$). There were significant decrease in the level of AST, ALT, GGT and LDH in two groups at postoperative 1st hour and postoperative 24th hour compared to preoperative values. There

was significant increase in INR values in the two groups at the postoperative 1st and 24th hour. N acetyl cysteine group showed statistically significant increase in glutathione S transferase levels compared to placebo group at the 1st hour of postoperative period. Postoperative 1st and 24th hour glutathione S transferase levels were significantly higher when compared to preoperative values. In placebo group, malondialdehyde levels showed no statistically significant changes at the postoperative 1st hour and postoperative 24th hr versus preoperative values. N acetyl cysteine group showed stastistically significant increase in malondialdehyde levels at the postoperative 1st hr and postoperative 24th hr compared to preoperative values .Finally in his study Beyez et al concluded that isoflurane anaesthesia along with N-acetyl cysteine has lesser effect on liver function than isoflurane alone.

2. Tomoki Nishiyama study revealed that postoperative hepatotoxicity and nephrotoxicity did not increase by either combination of isoflurane and sevoflurane and also with repeated propofol–fentanyl anaesthesia in 14 days to 1 year. Among the total patients, large number of patients who underwent surgery with isoflurane anaesthesia showed high serum levels of liver enzymes. Since it was a retrospective study, perioperative managements like antibiotics,

fluid management, temperature, respiration could not be controlled. It was a limitation to this study. As the second anaesthesia cannot be predicted before the first surgery it is not possible to perform this study in a prospective manner. They have extracted all information from patient records about anaesthesia and postoperative period, which will have some information missing. The type of surgery was not selected because the patients undergoing the same type of surgery twice were very few. Because of that there were significant differences in surgery duration and doses of anaesthetic agent between the groups and between the first and second anaesthesia.

3. Brunt et al reported a case with liver damage by repeated isoflurane anaesthesia.

4. Byles PH, Dobkin AB, Ferguson JH, Levy AA. Forane revealed that repeated isoflurane anaesthesia did not produce liver and renal damage in an animal study.

5. Nishiyama and Yokoyama had studied the effects of inhalation anaesthetic agents on liver and renal functions. In their studies, serum concentration of liver enzymes were increased by isoflurane anesthesia after the surgery more than compared with sevoflurane anaesthesia. They had also revealed that repeated anaesthesia with sevoflurane or isoflurane within 30-180 days had no possibility of

increased risk for liver and renal damage after the second anaesthesia compared to the first one. Sevoflurane and isoflurane both have the same action on hepatic blood flow and so the hepatic blood flow might not contribute to the difference in liver damage caused by anaesthesia with sevoflurane and isoflurane.

6. Iaizzo et al suggested that the G-protein of α_1-receptor of the cell membrane is modified by isoflurane, which induces calcium release from endoplasmic reticulum into the cytosol. The calcium accumulation is the cause for liver cell damage. Many factors like antibiotics, other drugs and fluid infusion administered in the postoperative period might have some effects on hepatic function. Analyzing these factors completely from the records was difficult but there was no significant differences in these factors.

7. Christ DD et al suggested that metabolism of enflurane forms covalently bound liver adduct proteins which reacts with antibodies from patients suffering from halothane hepatitis. Trifluroacetate might induce hypersensitivity to increase the level of liver enzymes after exposure to isoflurane for the second time.

8. Lind RC, Gandolfi AJ, Hall PM : A product of isoflurane metabolism, trifluoro acetic acid (TFA) combines with liver

microsomal protein and may initiate a antigen antibody reaction to produce hepatocellular damage like that of halothane.

9. Gunaratnam et al had reported a case of hepatitis caused by isoflurane due to its cross hypersensitivity with halothane.

10. Ohmori et al reported a case with significant increase of serum level of liver enzymes following sevoflurane anesthesia after isoflurane anesthesia. They suggested cross hypersensitivity to inhalation anaesthetics by a drug-induced lymphocyte stimulating test.

11. Takenami et al suggested that repeated anaesthesia with sevoflurane did not change metabolism of sevoflurane and induced no renal damage, while two of eight patients had increased concentration of liver enzymes after anaesthesia, especially after second time in one case in the study. In 27 cases out of 80 repeated sevoflurane anaesthesia, 11 liver damage and 5 renal damage were suspected, but all were transient and were not clinically significant

12. Martin JL. Volatile anaesthetics and liver injury –Metabolism of sevoflurane produces hexafluoroisopropanol, inorganic fluoride, and formaldehyde. Sevoflurane does not produce trifluroacetate and hence not considered as a cause for immune-mediated liver damage seen with other inhalation anaesthetics.

13. Yang et al compared the effects of isoflurane anaesthesia and propofol anaesthesia in cirrhotic patients undergoing hepatic resection. The postoperative hepatocellular damage, preservation of liver functions and proinflammatory cytokines are assessed.Aspartate aminotransferase levels and alanine aminotransferase levels are measured as a indicator of liver damage.Bilirubin,albumin levels and prothrombin time are observed as markers of liver function.Pro inflammatory cytokines like tumor necrosis factor α and interleukin 1 are assessed by enzyme linked immunosorbant assay as they play an important role in hepatic acute phase response to ischaemia reperfusion. Isoflurane anaesthesia causes decreased postoperative inflammatory response.
14. AashishPandit et al, Postoperative hepatic dysfunction can be caused by all halogenated anaesthetics. Hepatotoxicity is caused by antibodies directed against liver proteins. These liver proteins are altered by trifluoroacetyl or trifluoroacetyl-like metabolites formed by anaesthetics. Few case reports of hepatotoxicity associated with isoflurane anaesthesia are seen in literature.

15. Elnadry et al studied the effects of isoflurane, sevoflurane and propofol in child A and B classified adult cirrhotic patients.In isoflurane group (n=17 patients) there was significant increase in

total S. Bilirubin 2 days after surgery and was elevated for 14 days postoperatively. There was also significant increase in ALT, AST and decrease in serum albumin and prothrombin concentration at 3rd, 7th and 14th postoperative day

16. In an animal study by Arici et al done on rabbits, isoflurane causes substantial histopathological changes in the form of mild to moderate tissue damage in liver and kidneys.
17. Mansour et al studied the role of antioxidants in prevention of isoflurane-induced hepatotoxicity. Twenty-two patients belonging to Child Pugh class A, undergoing cholecystectomy were allotted into two groups. The anti oxidant group received 1gm/hr of N-acetyl cysteine infusion throughout the surgery, 1gm of vitamin C and 400 IU of vitamin E. whereas the saline group did not receive any.Intracellular adhesion molecule (ICAM-1) – mediates adhesion of lymphocytes to hepatocytes and causes inflammation of liver. Normally these molecules are absent in normal liver but can occur in a number of acute and chronic inflammatory conditions. Blood samples were obtained in all patients in the preoperative period, one hour, and one day after the operation. Blood samples were analyzed to determine serum ICAM-1, total proteins, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline

phosphatase, total and conjugated serum bilirubin. The authors demonstrated a significant increase in ICAM, AST and ALT levels in saline group compared to the antioxidant group. They concluded that the combination of antioxidant compounds is beneficial to ameliorate hepatotoxicity in cirrhotic patients undergoing general anesthesia. ICAM-1 may convey the degree of leucocyte adhesion, and hence reflects the severity of inflammatory activity. Therefore, it represents a good diagnostic or prognostic indicator of clinical importance for hepatic function.

18. Gatecel et al assessed the effects of halothane and isoflurane on Hepatic Arterial Blood Flow (HABF) and Portal Venous Blood Flow (PVBF), in six monkeys and humans using the pulsed Doppler technique. Patients were maintained with either 1% halothane or 1.5% isoflurane end tidal concentrations. Total hepatic blood flow was maintained with isoflurane and decreased by 36% in halothane group.

19. Nishiyama et al compared liver functions after sevoflurane and isoflurane anesthesia. The study included 90 patients who underwent neurosurgical patients. The patients were randomized to isoflurane and sevoflurane group each containing 45 patients. Serum concentrations of AST, ALT, total bilirubin, ALP, Gamma

GlutamylTranspeptidase(GTP) and LDH were measured 3days prior to surgery, 1,2,3,7,& 14 days after surgery. Serum concentrations of AST, ALT and GTP were higher after isoflurane than sevoflurane anesthesia. Despite modest blood and tissue solubility and its minimal metabolism, 45 reports of postoperative hepatic dysfunction were filed with Food and Drug Administration for anesthetics between 1981 and 1984. The reviewers found that the hepatic injuries in most of the cases were attributed to sepsis, hypoxia, biliary obstruction, nutritional deficiency, circulatory shock, viral hepatitis and erythromycin ingestion. The reviewers concluded that there was no reasonable association between administration of isoflurane and subsequent administration of hepatic dysfunction.

20. Ihtiyar et al reported a case of fulminant and fatal hepatic necrosis two days after open cholecystectomy in a 68-year-old man under isoflurane anesthesia. On the first postoperative day he developed tachypnea, tachycardia, and hypotension (70/40 mmHg) for 5 min. Lung scintigraphy showed small areas of irregular perfusion due to emboli. Treatment consisted of intravenous fluids, inotropic agents and heparin infusion. Two days postoperatively he developed right upper quadrant pain with fever, vomiting, and a rise in liver enzymes to twice the normal limit. Serum white blood cells was

18,100/ mm^3, serum bilirubin 3.8 mg/dl, alkaline phosphate 823 IU/L, AST 6200 IU/L, ALT 1900 IU/L, LDH 12,600 IU/L and INR peaked at 3.Three days postoperatively he developed abdominal distension, decreased mental status and agitation. Serum white blood cells peaked at 24,000/mm^3, AST 20,200 IU/L, ALT 7200 IU/L, LDH 20,730 IU/L, bilirubin 4.4 mg/dl and INR 3.7. Serological tests for hepatitis A, B and C were negative. Ultrasonography revealed normal portal, mesenteric and hepatic vascular systems and intrahepatic ducts.The next day the liver enzymes levels decreased to AST 7610 IU/L and ALT 431 IU/L, with anuria and bilateral pulmonary infiltrate. He developed multi-system organ failure and died on the sixth day postoperatively. On post-mortem liver wedge biopsy, there was confluent necrosis and sinusoidal congestion involving predominantly zones 3 and 2. There were zones of confluent bridging necrosis linking adjacent central veins as well. In some areas, necrosis extended to the entire hepatic lobule.

21. Kusuma et al reported fulminant hepatic failure after repeated exposure to isoflurane. A 6-year-old child developed fulminant hepatic failure 2 days following craniotomy under general anaesthesia. There was no evidence of viral, autoimmune, or metabolic causes of hepatitis. No other medications known to cause

hepatitis, except low dose paracetamol, were administered. The clinical and histological picture of this case was similar to halothane hepatitis

22. Peiris et al reported a case of fulminant hepatic failure in a 77 year old woman who underwent open right hemi colectomy under isoflurane anesthesia. Preoperative and intraoperative course was uneventful. On 2nd postoperative period patient started developing abnormal liver function tests and deteriorated over 2 days and died on 4th postoperative day as other supportive measures failed. Postmortem liver examination showed fulminant liver failure. Microscopically there was massive coagulative necrosis of the hepatocytes with a centrilobular pattern similar to halothane toxicity.

23. Nishiyama et al studied the effects of repeat exposure to inhalational anesthetics on liver and renal function. The adult patients who received general anesthesia two times within the interval of 14 days to 1 year were retrospectively analyzed. Those who received sevoflurane anaesthesia twice (SS group, 53 cases), isoflurane anaesthesia twice (II group, 31 cases), sevoflurane followed by isoflurane anaesthesia (SI group, 29 cases), isoflurane followed by sevoflurane anaesthesia (IS group, 35 cases), and propofol–fentanyl

anaesthesia twice (PP group, 58 cases) was enrolled. Serum concentrations of AST, ALT, total bilirubin, Gamma glutamyltranspeptidase(GGT), urea, creatinine were measured between first 16days after surgery.In the IS group, the number of the patients with abnormal values of ALT and GGT 5–8 days after surgery were significantly smaller at second anaesthesia compared to the first anaesthesia. The number of the patients with abnormal values of AST, ALT, and GGT were significantly larger in the II group than the SS and PP groups.

24. D. Adam algren, M.D. Review of n-acetylcysteine for the treatment of Acetaminophen toxicity in paediatrics. Acetaminophen (paracetamol) toxicity is a common cause of drug-induced hepatotoxicity in children and adults. N acetyl cysteine (NAC) for several decades has been proven to be the antidote of choice in treating paracetomol induced hepatotoxicity. Oral and intravenous N acetyl cysteine are equally effective in preventing hepatotoxicity caused by acetaminophen. There is significant clinical evidence to prove their efficacy. The most important factor in assessing the efficacy of N acetyl cysteine is the timing of starting the therapy in relation to the drug ingestion. Patients taking acute overdose of paracetamol and having N acetyl cysteine therapy being started

within 8 hours of ingestion have better prognosis and they have less than 10% incidence of liver toxicity and they generally do not develop liver failure or die. Those patients who ingest excessive doses of paracetamol chronically over several hours and patients in whom N acetyl cysteine therapy was started more than 8 hours after an acute drug intake have 8-50% incidence of hepatotoxicity. Patients who have delayed initiation of N acetyl cysteine therapy are at high risk of developing fulminant hepatic failure and death than the patients in whom N acetyl cysteine is given earlier within 8 hrs. The preferred route for N acetyl cysteine therapy unless any contraindications (e.g aspiration, persistent vomiting) exist is the oral route. The recommended loading dose is 150mg/kg followed by a maintenance dose of 70 mg/kg orally given every 4 hours. This dosing regime is recommended to be continued for 72 hours. The patients those who are not able to tolerate oral administration of N acetyl cysteine or have fulminant hepatic failure are recommended to be initiated on intravenous N acetyl cysteine. The commonly used protocol for intravenous administration of N acetyl cysteine is to administer 150 mg/kg IV over 1 hour,which is then followed by 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. In pediatric patients (weighing less than 40 kg) it is recommended to

have a modified intravenous dosing formulation to prevent excessive fluid administration. The efficacy of N acetyl cysteine as a antidote is determined by great extent to the time that treatment is initiated after an overdose of acetaminophen. NAC therapy should be initiated within 8 hours of an acute ingestion and otherwise as soon as possible. In cases of hepatotoxicity, NAC should be continued until the serum liver transaminases fall to less than 1000 IU/L, bilirubin and coagulation studies are normal, and the patient is clinically well." Both oral and intravenous NAC are well tolerated. Nausea and vomiting were seen as a common side effects of oral dose of NAC. Intravenous injections of NAC have rarely caused anaphylactoid reactions. Mild rash, flushing and urticaria were the common reactions seen with i.v dose of NAC. They can be treated easily with antihistamines and most of the time infusion can be completed without any problem. Life-threatening anaphylactoid reactions and mortality is very rare.

25. Appelboam et al reported a case of serious anaphylactoid reaction to i.v. dose of NAC patient suffering from asthma. This case report showed that the preexisting asthma warrants a careful administration of intravenous N acetyl cysteine.

26. Bailey and McGuigan had done a review of paracetamol toxicity charts for studying the management of anaphylactoid reactions due to NAC and to form guidelines about continuing the therapy, whether clearly indicated and needed. They reported a 23% reaction rate in the 20-hr intravenous protocol, 20% reaction rate in the 48-hr intravenous protocol, and no reactions in the 72-hr oral protocol. Treatment guidelines were formed and followed prospectively in the regimen of NAC treatment for paracetomol poisoning. The treatment protocol ranged from no intervention for simple flushing, maintenance of airway and circulation, intravenous diphenhydramine injection, oral dose of cimetidine and ephedrine in the cases of hypotension and respiratory symptoms. Even in these cases, NAC was restarted in 1 hr if no symptoms recurred. To conclude, the treatment guidelines were followed successfully with no evidence of poor outcome. The limitations of this study was it was done on only 33 patients and life threatening serious complications did not occur.

MATERIALS AND METHODS

After instituitional ethical committee approval the study was conducted in 60 patients. ASA I and II Patients scheduled for elective laparoscopic surgeries under general anaethesia were eligible for the study. After getting consent, the anaesthetic technique was performed.

TYPE OF STUDY :

It was a prospective randomized controlled double blinded study.

SELECTION OF PATIENTS

INCLUSION CRITERIA

The patients selected for this study were of age group from 18 to 60 yrs, ASA I and II Patients of both sexes are included in the study. Patients undergoing laparoscopic appendicectomy and hernioplasty were included in the study.

EXCLUSION CRITERIA

The patients exhibiting the following features are excluded from the study

-Patients with severe cardiovascular, pulmonary, renal, hepatic, endocrine, neuropsychiatric diseases.

-History of using Coumadin recently.

-Patient on aspirin,NSAIDS,corticosteroids,immune depressants.

-Patient with history of asthma and drug or alcohol abuse.

-Patient with history of Hepatitis B or C

-Patient with history of abdominal surgery in past 5 yrs.

-Patient's refusal.

PREOPERATIVE PREPARATION

All patients are premedicated with injection Glycopyrrolate 10 µg/kg i.v 15 minutes prior to induction.

The patients were allocated into two groups in a randomized manner

GROUP P -Placebo group (Isoflurane with normal saline)

GROUP N –N acetyl cysteine group (N acetyl cysteine with isoflurane)

PROCEDURE DETAILS:

After shifting the patient inside the operating room, they are monitored with standard 3 lead electrocardiogram, pulseoximetry, and automatic cuffed noninvasive blood pressure were connected. Basal values of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation are noted. After securing intravenous line, in a randomized manner 30 patients in Group N were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline while 30 patients in Group P received only 250 ml of 0.9% normal saline before induction. All patients are preoxygenated with 100% oxygen. All patients are induced with injection thiopentone sodium 5mg/kg, injection fentanyl 2µg/kg and injection succinylcholine 1.5 mg/kg. Patients were intubated and connected to ventilator after 3 minutes. Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen with 1-2% isoflurane in fresh gas

flow of 6l/min. Tidal volume delivered was about 8-10ml/kg with a frequency of 10-12/min. Neuromuscular blockade was maintained with injection atracurium.

Volatile anaesthetic concentration was adjusted to maintain the mean arterial blood pressure and heart rate within 20% of preinduction values. In case of signs of light anaesthesia(lacrimation,sweating or flushing) isoflurane concentration is increased by 0.5% to 2%.Atropine 0.6mg was given intravenously if heart rate dropped less than 45 beats per minute. In case of hypotension not responding to intraoperative replacement of fluids or bradycardia not responding to treatment, then isoflurane concentration is reduced. Blood pressure was maintained above 80mmhg throughout the procedure to prevent liver damage.

After the last skin suture, nitrous oxide and isoflurane were discontinued.Injection neostigmine 40µg/kg and injection Glycopyrrolate 10 µg/kg were used to reverse the residual neuromuscular blockade. Trachea was extubated when the regular spontaneous breathing pattern was returned and when the patients were able to open their eyes on command. Perioperative complications like nausea, vomiting, flushing, rash, urticaria, cough and hypotension were noted.

PARAMETERS MONITORED:

These parameters were observed in preoperative period, postoperative 1st hr and postoperative 24th hr from peripheral venous blood.

Serum bilirubin

Aspartate aminotransferase

Alanine aminotransferase

Lactate dehydrogenase

Prothrombin time

Perioperative side effects were also noted.

STATISTICAL METHOD

Descriptive analysis was done in terms of proportions for categorical variables and in terms of mean and standard deviation for continuous variables. Baseline characteristics between the two groups were compared using chi square test for categorical variables and using independent samples t test for continuous variables.

The difference between baseline value and 1 hour value for LFT was calculated and the differences between the two groups were tested by unpaired t test. Similarly the difference between baseline value and 24 hour value for all LFT parameters was calculated and the difference between the two groups was compared using unpaired t test. This method is called testing the difference in differences. A p value of <0.05 was considered statistically significant. All data were entered in Microsoft Excel and analyzed using Stata version 12.

RESULTS

A:PROFILE OF CASES STUDIED

TABLE 1 : AGE DISTRIBUTION

AGE GROUP	**GROUP P (n = 30)**		**GROUP N (n = 30)**	
	N	**%**	**N**	**%**
21-30 years	16	53.3	17	56.7
31-40 years	9	30.0	10	33.3
41-50 years	5	16.7	3	10.0
TOTAL	**30**	**100**	**30**	**100**
MEAN	32.03		30.93	
SD	9.89		8.62	
P VALUE	0.747			
	Not significant			

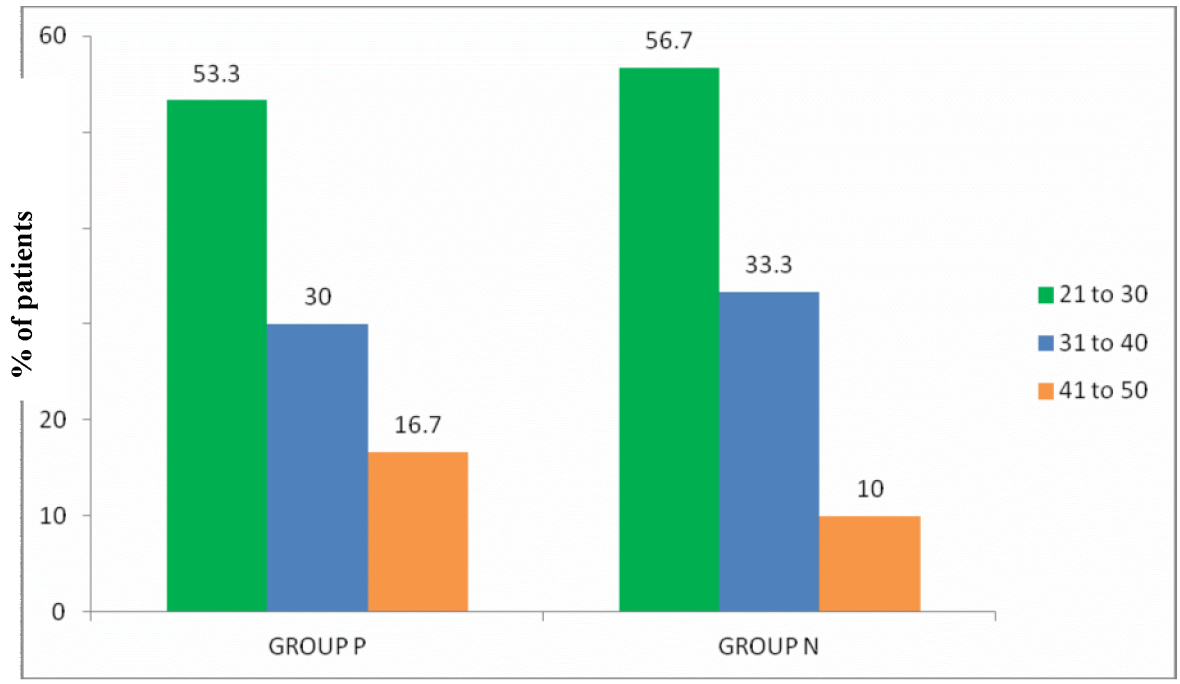
There was no statistically significant difference in age between the two groups.

TABLE 2 : SEX DISTRIBUTION

SEX	**GROUP P (n = 30)**		**GROUP N (n = 30)**	
	N	**%**	**N**	**%**
MALE	20	66.7	21	70
FEMALE	10	33.3	9	30
TOTAL	**30**	**100**	**30**	**100**
P VALUE	0.781			
	Not significant			

The sex composition of the two groups was identical without any significant difference.

AGE DISTRIBUTION



SEX DISTRIBUTION

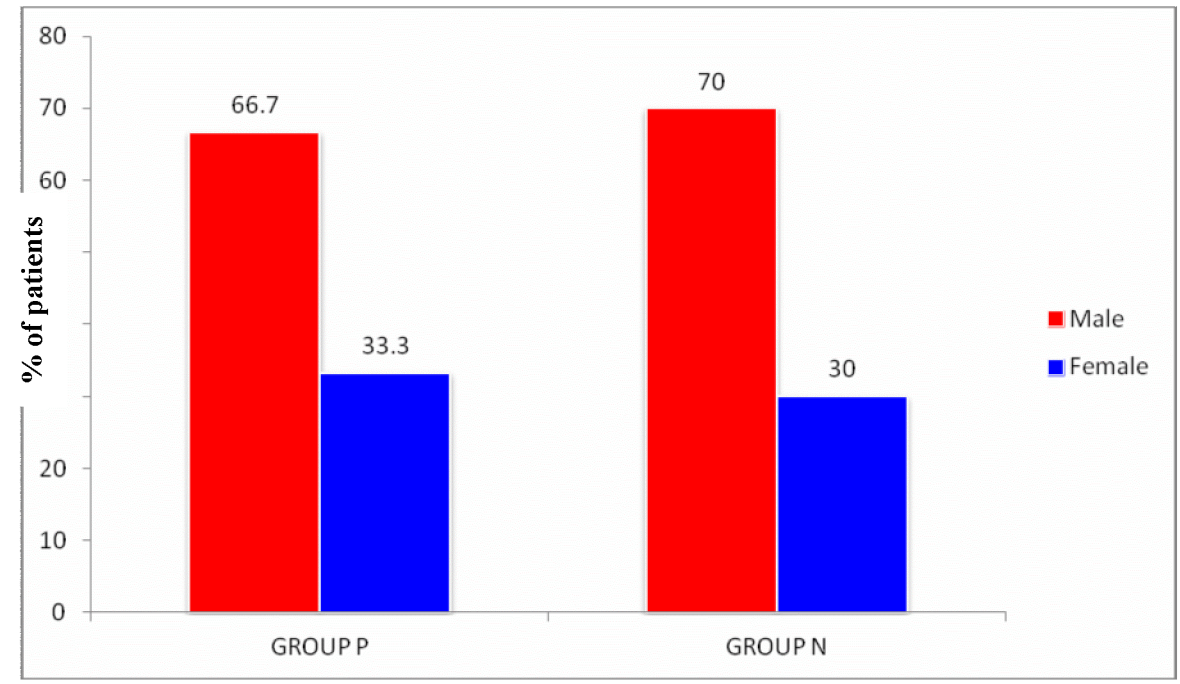


TABLE 3 : TYPE OF SURGERY

Type of surgery	**GROUP P (n = 30)**		**GROUP N (n = 30)**	
Lap Appendicectomy	24	80.0	25	83.3
Lap Hernioplasty	6	20.0	5	16.7
TOTAL	**30**	**100**	**30**	**100**
P VALUE	0.739			
	Not significant			

There was no any difference in the type of surgery between placebo group and N acetyl cysteine group.

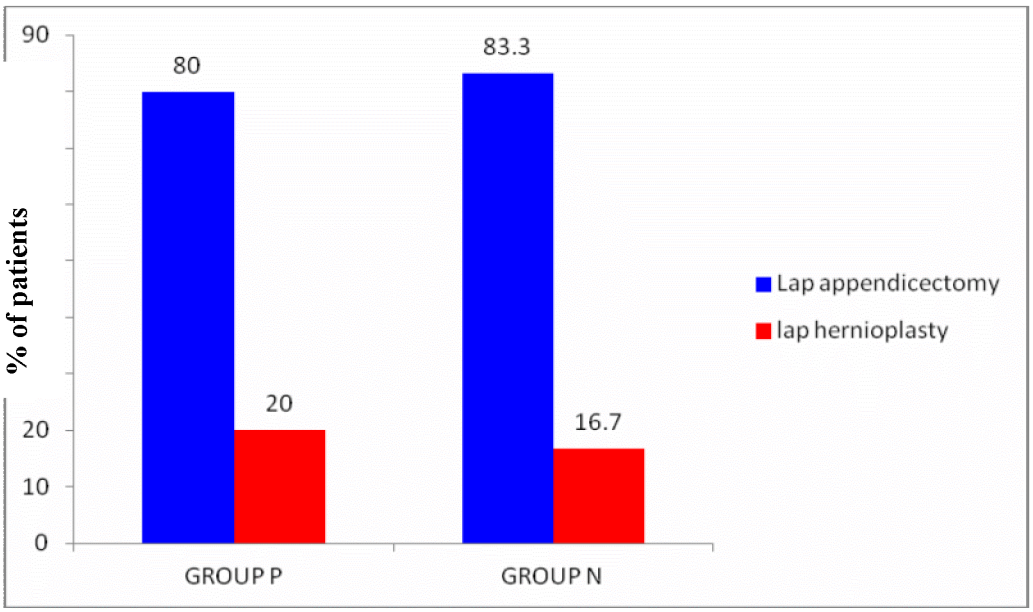
TABLE 4 : ASA STATUS

ASA	**GROUP P (n = 30)**		**GROUP N (n = 30)**	
I	24	80	26	86.66
II	6	20	4	13.33
TOTAL	**30**	**100**	**30**	**100**
P VALUE	0.488			
	Not significant			

There was no significant difference in the ASA status of the two groups.

(P value>0.05)

TYPE OF SURGERY



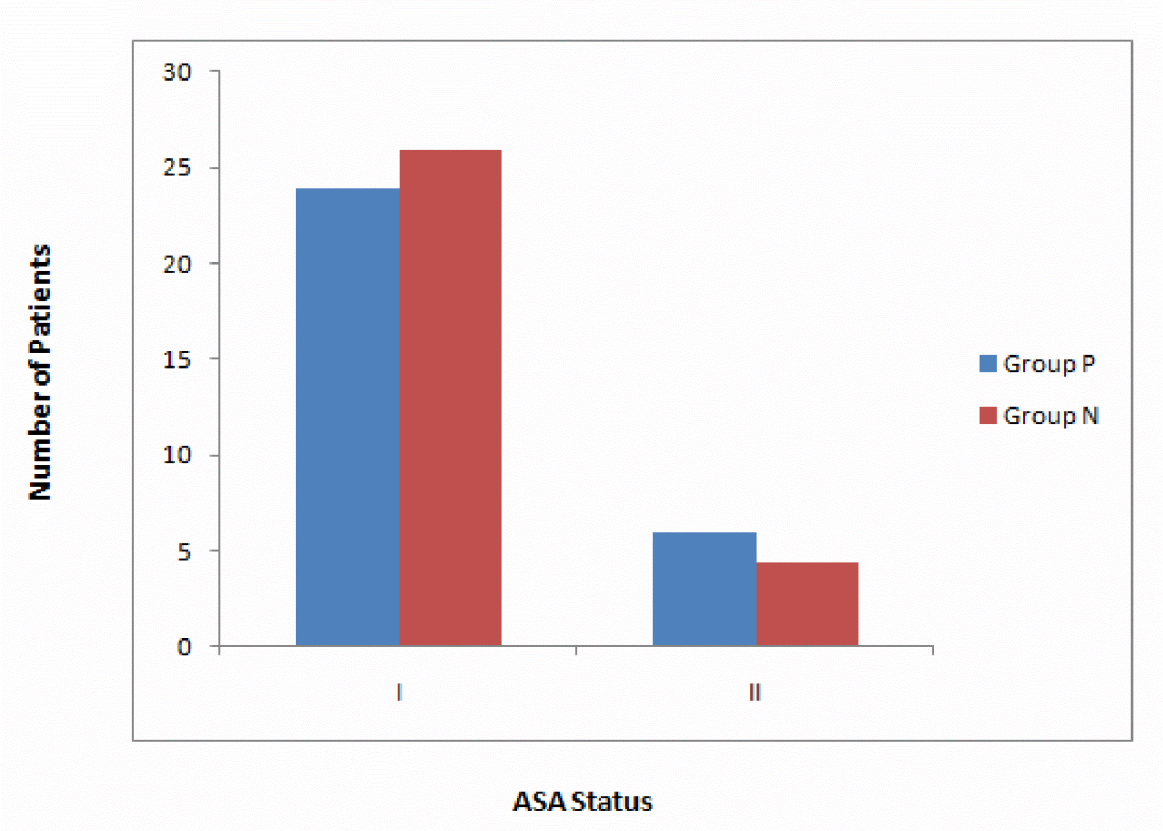


TABLE 5 : WEIGHT

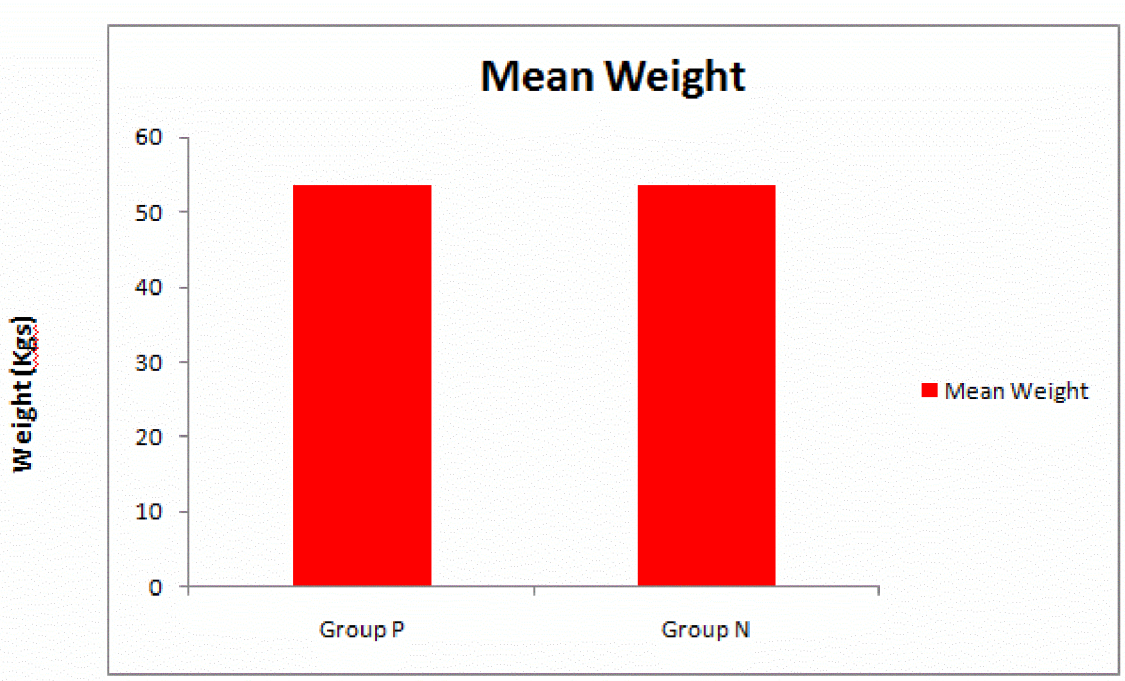
PARAMETER **WEIGHT**	**GROUP P** **(kg)**	**GROUP N** **(kg)**
MEAN	53.53	53.53
SD	7.81	7.51
P VALUE	**0.712** **NOT SIGNIFICANT**	

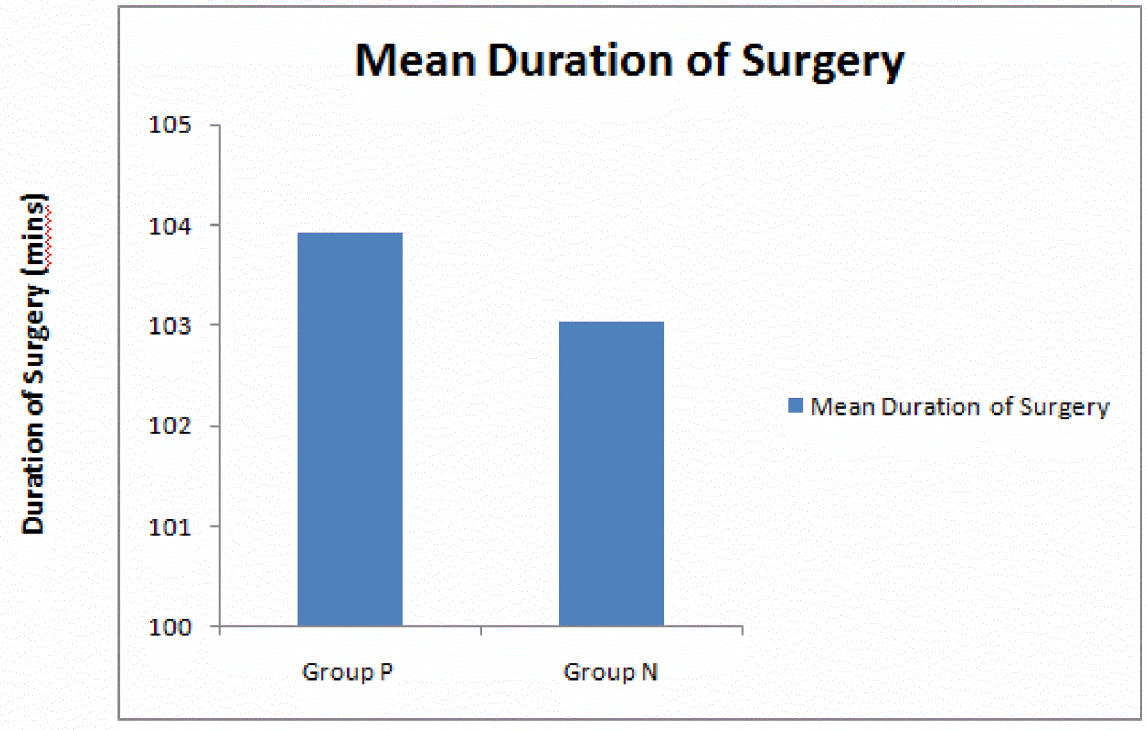
There was no difference in weight of the patients between the two groups.

TABLE 6 : DURATION OF SURGERY

PARAMETER **DURATION OF SURGERY**	**GROUP P** **(minutes)**	**GROUP N** **(minutes)**
MEAN	103.93	103.03
SD	13.64	12.86
P VALUE	**0.793** **NOT SIGNIFICANT**	

Duration of surgery between the two groups does not show any significant difference .($p>0.05$)


Mean Weight
Weight (kgs)
60
50
40
30
20
10
0
Group P
Group N
Mean Weight


Mean Duration of Surgery
Duration of Surgery (mins)
105
104
103
102
101
100
Group P
Group N
Mean Duration of Surgery

B : PARAMETERS MONITORED

TABLE 7a : BILIRUBIN

PARAMETER BILIRUBIN mg/dl	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	0.86	0.1	0.83	0.1
POSTOPERATIVE 1ST HR LEVEL	0.863	0.1	0.84	0.1
P VALUE	0.470 NOT SIGNIFICANT			

Statistically there is no any significant difference in bilirubin levels between Group P and Group N at postoperative 1st hour.

TABLE 7b : BILIRUBIN

PARAMETER BILIRUBIN mg/dl	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	0.86	0.1	0.83	0.1
POSTOPERATIVE 24^{TH} HR	0.876	0.1	0.843	0.1
P VALUE	0.550 NOT SIGNIFICANT			

Bilirubin levels after 24 hours postoperative period does not show any significant difference between two groups.

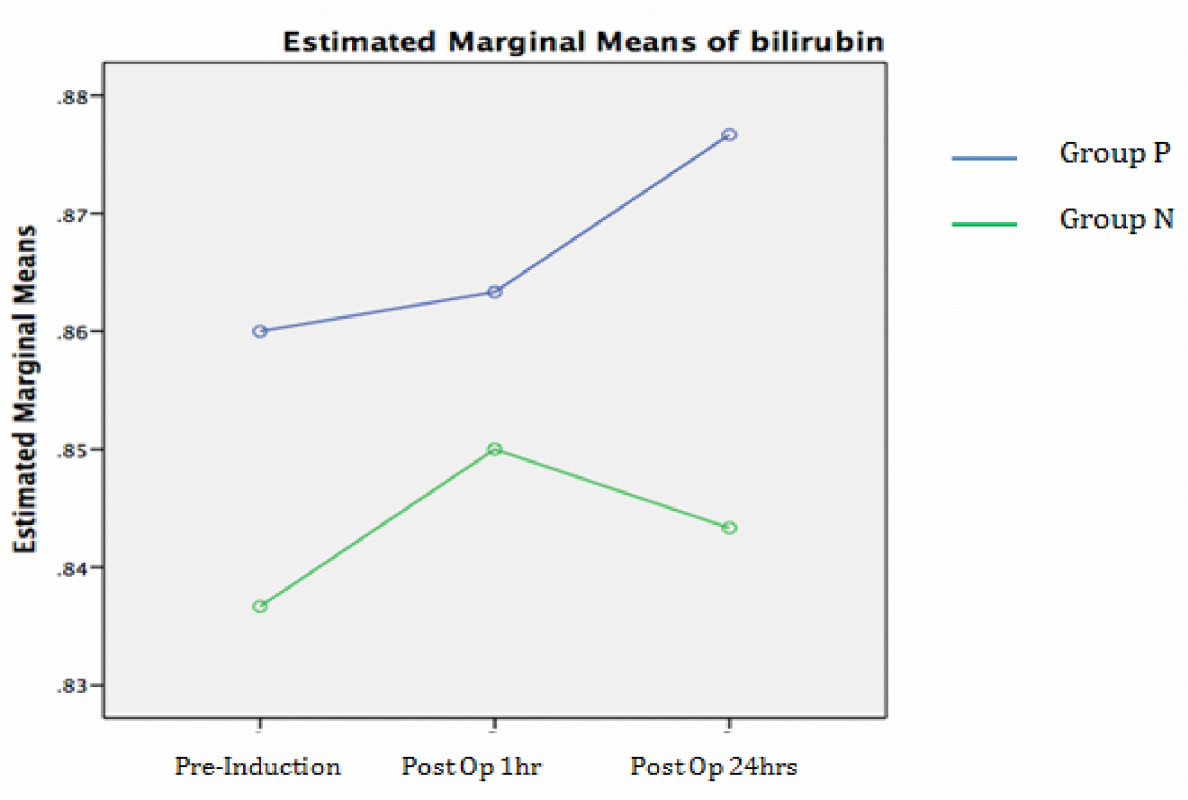

Estimated Marginal Means of bilirubin
Estimated Marginal Means
.88
.87
.86
.85
.84
.83
Pre-Induction
Post Op 1hr
Post Op 24hrs
Group P
Group N

TABLE 8a : ASPARTATE AMINOTRANSFERASE

PARAMETER ASPARTATE AMINOTRANSFERASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION AST LEVEL	26.16	10	24	10
POSTOPERATIVE 1 HR AST LEVEL	29.66	12	25	10
P VALUE	0.094 NOT SIGNIFICANT			

There is no significant difference in AST levels postoperatively after one hour between the two groups and the P value is insignificant.

TABLE 8b : ASPARTATE AMINOTRANSFERASE

PARAMETER ASPARTATE AMINOTRANSFERASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVELS	26.16	10	24	10
POSTOPERATIVE 24th HR LEVELS	31.23	13	25.2	10
P VALUE	0.059 NOT SIGNIFICANT			

In Group P there is a rise in AST levels during postoperative 24th hour compared to Group N. But the p value is not significant. There is no statistically significant difference in AST levels between two groups in postoperative 24th hour.

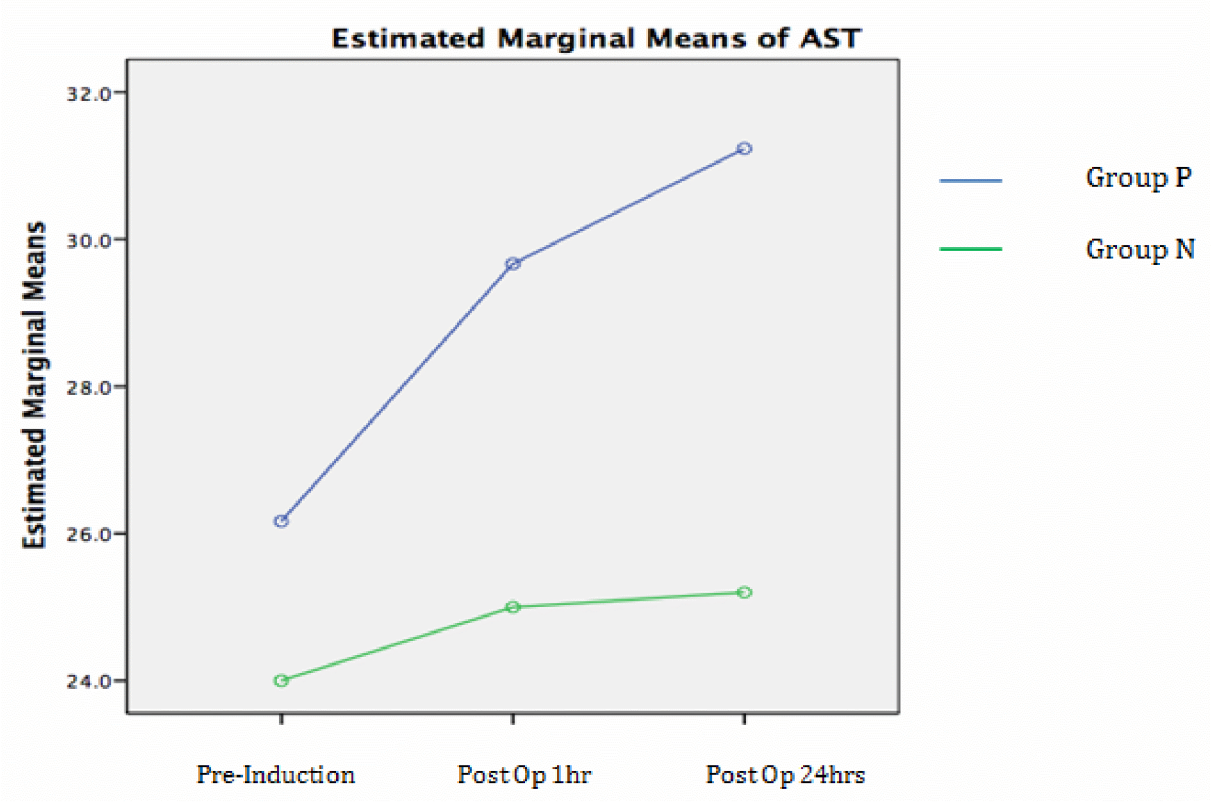

Estimated Marginal Means of AST
Estimated Marginal Means
32.0
30.0
28.0
26.0
24.0
Pre-Induction
Post Op 1hr
Post Op 24hrs
Group P
Group N

TABLE 9a: ALANINE AMINOTRANSFERASE

PARAMETER ALANINE AMINOTRANSFERASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	21.5	11	22.43	11
POSTOPERATIVE 1ST HR LEVEL	21.1	11	22.1	9
P VALUE	0.954 NOT SIGNIFICANT			

ALT levels show a decrease at postoperative 1st hour in both groups it is not stastistically significant.

TABLE 9b : ALANINE AMINOTRANSFERASE

PARAMETER ALANINE AMINOTRANSFERASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	21.5	11	22.43	11
POSTOPERATIVE 24TH HR LEVEL	21.86	14	22.83	10
P VALUE	O.064 NOT SIGNIFICANT			

Alanine aminotransferase levels after postoperative 24 hours in group P and group N does not show any stastistically significant difference.(P value > 0.05)

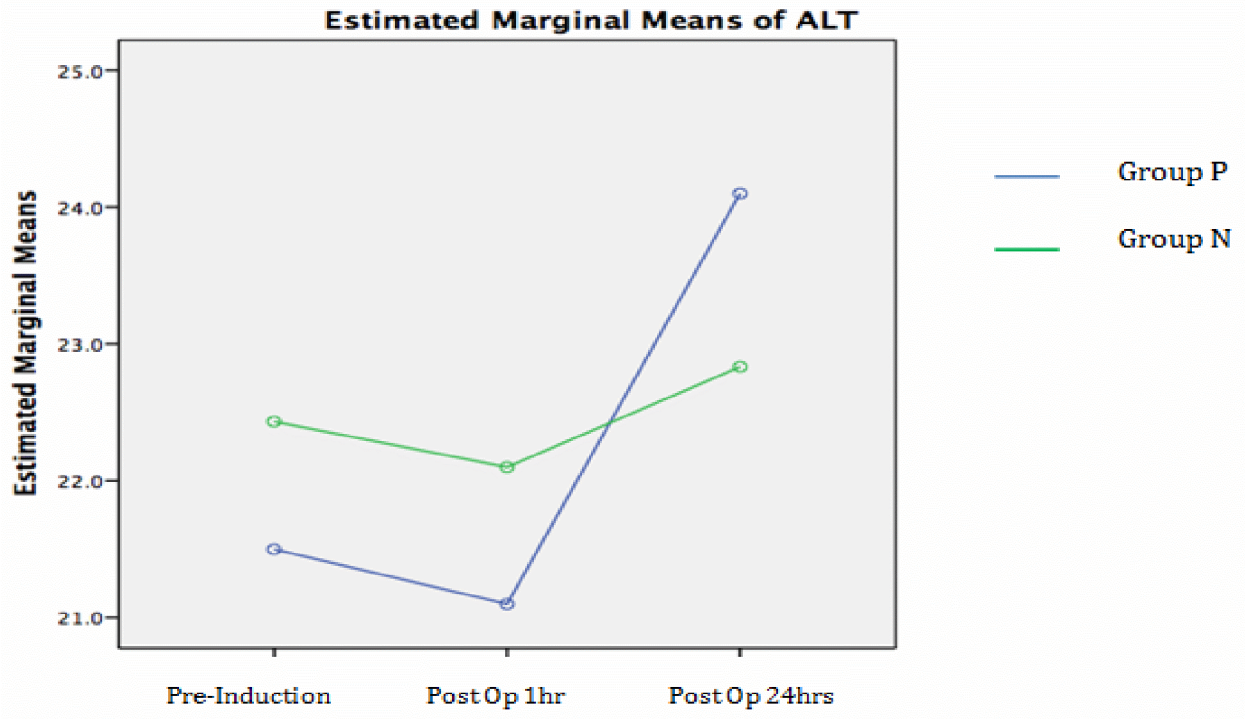

Estimated Marginal Means of ALT
Estimated Marginal Means
25.0
24.0
23.0
22.0
21.0
Pre-Induction
Post Op 1hr
Post Op 24hrs
Group P
Group N

TABLE 10a : LACTATE DEHYDROGENASE

PARAMETER LACTATE DEHYDROGENASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	177.6	54	160.5	62
POSTOPERATIVE 1ST HR LEVEL	188.2	64	171.2	70
P VALUE	0.901 NOT SIGNIFICANT			

Lactate dehydrogenase levels in both groups show a rise after 1 hour of postoperative period which is not statistically significant.

TABLE 10b : LACTATE DEHYDROGENASE

PARAMETER LACTATE DEHYDROGENASE IU/L	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	177.6	54	160.5	62
POSTOPERATIVE 24TH HR LEVEL	184.7	57	163.96	62
P VALUE	0.734 NOT SIGNIFICANT			

There is no any stastistically significant difference between postoperative level of lactate dehydrogenase

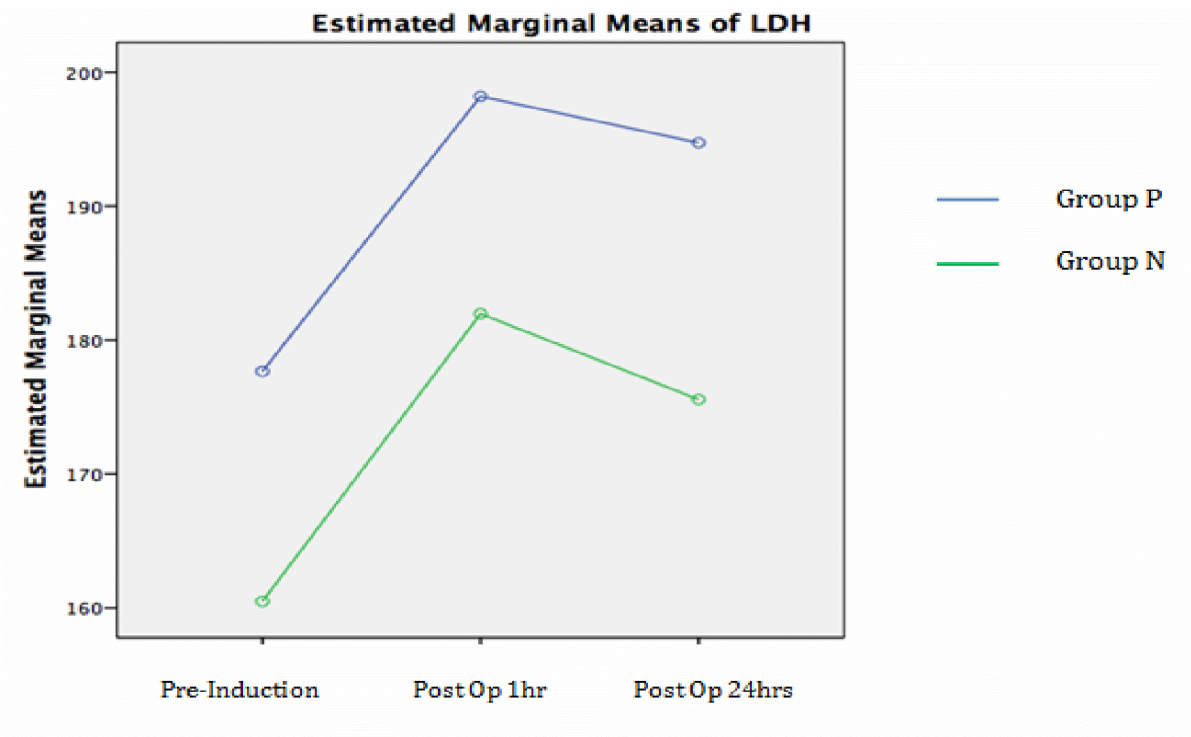

Estimated Marginal Means of LDH
Estimated Marginal Means
200
190
180
170
160
Pre-Induction
Post Op 1hr
Post Op 24hrs
Group P
Group N

TABLE 11a: PROTHROMBIN TIME

PARAMETER PROTHROMBIN TIME (SEC)	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	12.83	1	12.9	1
POSTOPERATIVE 1ST HR LEVEL	12.8	1	12.66	1
P VALUE	0.419 NOT SIGNIFICANT			

There is no significant difference in prothrombin time between the placebo group and N acetyl cysteine group after first hour of postoperative period.

TABLE 11b: PROTHROMBIN TIME

PARAMETER PROTHROMBIN TIME (SEC)	GROUP P (PLACEBO GROUP)		GROUP N (N ACETYL CYSTEINE GROUP)	
	MEAN	SD	MEAN	SD
PREINDUCTION LEVEL	12.83	1	12.9	1
POSTOPERATIVE 24^{TH} HR LEVEL	12.9	1	12.5	1
P VALUE	0.556 NOT SIGNIFICANT			

There is no significant difference in prothrombin time between the placebo group and N acetyl cysteine group after 24 hrs postoperative period.

Estimated means of prothrombin time

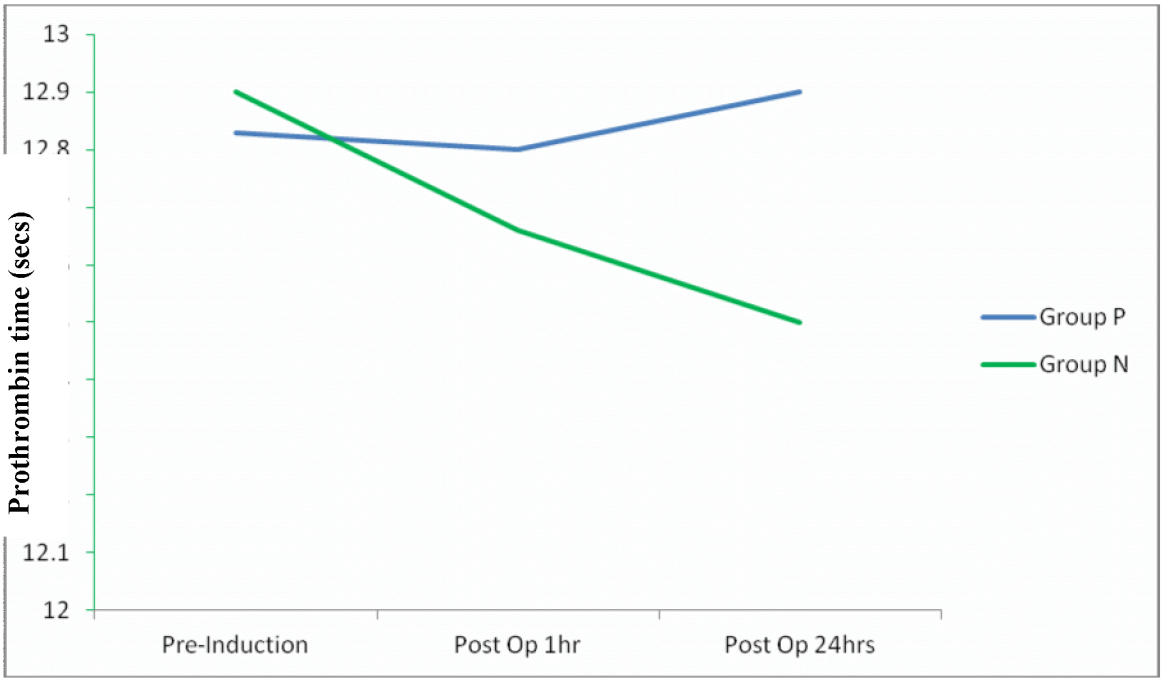


TABLE 12 : COMPLICATIONS

COMPLICATION	GROUP P	GROUP N
NAUSEA	5	4
RASH	0	2
URTICARIA	0	1
HYPOTENSION	4	5
ANAPHYLACTOID REACTION	0	0

Complications like nausea and hypotension are comparable between the two groups. Rash and urticaria occurred only in two patients and one patient in N acetyl group respectively which was treated with antihistaminic medication.

DISCUSSION

The common organ to be affected by drug toxicity is liver. Because, it is where the drug get metabolized. In this study with isoflurane no adverse effect on liver was seen.

Preoperative liver function tests are usually not indicated, unless there is some history related to hepatic injury or any clinical signs during examination related to it. Hence, pre-operative liver function tests are not done routinely. It should be based on history and physical examination.

Nishiyama et tal in their study found that there is postoperative decrease in AST, ALT levels after usage of volatile agents. Wissing H and Kuhr I showed insignificant decrease in level of ALT and AST postoperatively in children anaesthetized with desflurane.

In a study conducted by Beyez et al there was stastistically significant decrease in levels of AST,ALT,GGT,LDH at postoperative 1^{st} hour and 24^{th} hour in patients who underwent laparoscopic gynaecological procedures with isoflurane anaesthesia. There was significant increase in prothrombin time at postoperative 1^{st} hour and 24^{th} hour. Significant increase in levels of glutathione S transferase is seen in N acetyl cysteine group compared to isoflurane group proving the antioxidant effects of N acetyl cysteine.

In this study ALT and LDH levels showed a non-significant decrease in postoperative period. But AST levels in post-operative period showed non-significant rise which is contradictory to the results of previous studies.

In another study conducted by Yokoyama T and Nishiyama T comparing the effects of sevoflurane and isoflurane on neurosurgical patients, had found that in isoflurane group there is a peak increase in AST, ALT, GGT and LDH levels on 7^{th} day after surgery. But this increase is not statistically significant.

In both sevoflurane and isoflurane group prothrombin time showed significant increase during post-operative 1^{st} hour and post-operative 24^{th} hour. PTT levels were within normal range.

In this study, rise in aspartate transaminase levels correlates with the result of above mentioned study but it is not statistically significant. Prothrombin time did not show any significant change as happened in above mentioned study.

An imbalance between endogenous antioxidant mechanisms and free oxygen radicals is the cause for oxidative stress. N acetyl cysteine is a commonly used antioxidant against this oxidative stress. N acetyl cysteine has both direct antioxidant effect and indirect action by increasing glutathione stores.

It reacts directly with hydroxyl ions and deactivates them. A study conducted by Tepel M et al showed that glutathione significantly decreases contrast induced nephrotoxicity in high risk patients undergoing computerized tomography.

Hepatic blood flow is decreased in a dose dependant manner by all volatile agents. An important mechanism is raised sympathetic tone of the vena caval system, due to controlled ventilation. Isoflurane partially decreases portal blood flow but increases hepatic arterial flow.

Hypoxic environment can increase the risk of hepatic injury. But in this study the mean arterial pressure was maintained above 80mmhg to prevent hypoxic liver damage.

SUMMARY

The aim of the study is to prospectively compare the effects of isoflurane and N-acetyl cysteine with isoflurane on liver function in laparoscopic surgery patients during general anaesthesia. 60 ASA 1 and 2 patients were randomized into two groups. In a randomized manner 30 patients were given N-acetyl cysteine 150mg/kg in 250 ml 0.9% normal saline(Group N) while 30 patients received only 250 ml of 0.9% normal saline(Group P) before induction.Both the groups were induced with a standard intravenous induction technique. Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen with 1-2% isoflurane in fresh gas flow of 6l/min. Tidal volume delivered was about 8-10ml/kg with a frequency of 10-12/min. Neuromuscular blockade was maintained with injection atracurium. The mean arterial pressure was maintained above 80mmhg to prevent hypoxic liver damage. Atropine 0.6mg was given intravenously if heart rate dropped less than 45 beats per minute. In case of hypotension not responding to intraoperative replacement of fluids and treatment of bradycardia then isoflurane concentration is reduced. After the last skin suture, nitrous oxide and isoflurane were discontinued. Injection neostigmine 40µg/kg and injection and glycopyrrolate 10 µg/kg were used to reverse the residual neuromuscular blockade.Trachea was extubated when the regular spontaneous breathing pattern was returned and when the

patients were able to open their eyes on command. Perioperative complications like nausea, vomiting , flushing, urticaria,cough,bradycardia and hypotension were noted.

Parameters monitored were serum bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, prothrombin time before induction and in postoperative period at 1st and 24th hour.

The following results were obtained of the two groups compared,

1.Patient characteristics were comparable in both the groups.

2.Bilirubin and prothrombin time did not significantly change in the two groups at postoperative period.

3.Alanine aminotransferase levels showed a little decrease in both groups during postoperative 1st hour but not statistically significant.

4.Lactate dehydrogenase levels did not show any significant difference in both the groups.

5.Aspartate aminotransferase levels were increased in both the groups during the postoperative period but was not statistically significant.

CONCLUSION

Liver functions are well preserved in patients receiving isoflurane alone and in patients receiving isoflurane with N-acetyl cysteine. Hence infusion of N-acetyl cysteine does not offer any benefit in patients receiving isoflurane anaesthesia.

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PROFORMA

NAME : I.P.NO:

ASA:

AGE & SEX:

WEIGHT :

DATE & TIME OF ADMISSION:

DATE& TIME OF DISHARGE:

DIAGNOSIS:

PROCEDURE:

HISTORY: ALLERGY TO DRUGS, BLEEDING

DISORDERS, LIVER PATHOLOGY.

CLINICAL EXAMINATION: PR,BP, SPO2, RS, CVS.

BASIC INVESTIGATIONS:

HAEMOGLOBIN

RENAL PARAMETERS & SERUM ELECTROLYTES,

CHEST X RAY PA VIEW

ANAESTHETIC TECHNIQUE: Anaesthetic was maintained with 1-2% isoflurane with 50% oxygen-50% N2O at 6L/min by inhalation.

GROUP N : Patients received 150mg/kg NAC in 250ml 0.9% normal saline before induction.

GROUP P : Patients received 250ml of 0.9% normal saline before induction

LIVER FUNCTION TEST :

	Before induction	Postoperative 1 hr	Postoperative 24 hr
Total bilirubin			
AST			
ALT			
LDH			
Prothrombin time			

SIDE EFFECTS :

MASTER CHART (ISOFLURANE ALONE - PLACEBO GROUP)

S.No.	name	group	age	sex	wt	duration	typeofsur	asa	prebili	preast	prealt	preldh	preptt	post1bili	post1ast	post1alt	post1ldh	post1ptt	post24bili	post24ast	post24alt	post24ldh	post24ptt	Complication
1	KANIMOZHI	P	21	F	57	90	APPENDICECTOMY	I	0.9	38	18	150	12	0.9	36	20	214	12	0.9	42	22	230	12	Hypoten
2	SANDHANAM	P	50	M	60	104	APPENDICECTOMY	II	0.8	35	28	234	14	0.8	40	22	244	14	0.8	40	38	224	13	Nause
3	MANIKANDAN	P	26	M	42	93	APPENDICECTOMY	I	1	45	48	126	10	0.9	46	36	130	11	1	42	46	132	10	
4	ALBERT	P	28	M	47	110	APPENDICECTOMY	I	0.9	22	14	235	12	0.9	28	18	245	13	0.9	32	18	236	12	Nause
5	RAMESH	P	26	M	40	87	APPENDICECTOMY	I	0.7	27	52	186	13	0.7	32	50	260	13	0.7	28	52	206	13	
6	KANNAN	P	44	M	56	121	**HERNIOPLASTY**	II	0.7	23	19	156	14	0.7	35	15	160	13	0.7	48	15	164	14	Hypoten
7	JEYAMURUGAN	P	34	M	48	98	APPENDICECTOMY	I	0.8	51	28	234	13	0.8	50	16	244	12	0.8	51	36	264	13	
8	CHITTU	P	25	M	42	100	APPENDICECTOMY	I	1	39	42	142	14	1	36	49	164	11	0.9	35	56	138	12	
9	RAJESWARI	P	24	F	55	90	APPENDICECTOMY	I	0.8	45	40	235	14	0.8	56	32	238	14	0.8	60	52	252	13	
10	JANAKI	P	50	F	57	86	APPENDICECTOMY	I	0.9	27	33	186	12	0.9	60	38	260	14	0.9	61	46	206	14	
11	RAJ	P	50	M	64	126	**HERNIOPLASTY**	II	0.8	36	21	106	13	0.9	42	17	103	13	0.9	54	15	136	13	Nause
12	CHELLAPANDI	P	38	M	62	130	**HERNIOPLASTY**	I	0.7	36	30	131	14	0.7	40	36	130	14	0.8	24	36	157	14	
13	VEERANAM	P	40	M	55	115	APPENDICECTOMY	I	0.9	18	19	132	12	1	26	24	140	13	1	42	26	140	13	Hypoten
14	RAJENDRAN	P	50	M	58	127	**HERNIOPLASTY**	II	0.9	19	20	210	11	0.9	23	26	212	10	0.9	26	28	246	11	
15	SUGANYA	P	21	F	48	96	APPENDICECTOMY	II	0.9	16	16	214	12	1	30	18	222	11	1.1	36	18	201	11	
16	MOORTHY	P	38	M	70	134	**HERNIOPLASTY**	I	0.8	17	15	143	12	0.8	18	14	136	12	1	18	14	131	13	
17	NAGAJOTHI	P	24	F	47	106	APPENDICECTOMY	I	1	19	14	106	13	1	19	16	109	13	0.9	20	16	116	14	
18	SARAMMAL	P	38	F	56	102	APPENDICECTOMY	I	0.9	21	13	152	14	0.9	20	11	154	14	1	19	11	169	14	Nause
19	SAROJA	P	27	F	52	92	APPENDICECTOMY	II	0.7	19	12	126	14	0.7	22	13	132	13	0.8	24	13	128	14	
20	KARTHIGAISAMY	P	29	M	61	100	APPENDICECTOMY	I	0.9	17	18	186	13	0.9	26	16	260	14	0.9	28	15	206	13	Hypoten & Naus
21	JEYAKODI	P	31	F	67	124	**HERNIOPLASTY**	I	0.9	16	11	103	14	0.9	16	13	113	14	0.9	17	13	113	14	
22	LAKSHMI	P	36	F	62	95	APPENDICECTOMY	I	0.7	19	12	106	14	0.7	16	11	109	14	0.7	16	11	109	14	
23	LOGESWARAN	P	32	M	60	98	APPENDICECTOMY	I	0.8	22	14	141	13	0.8	23	12	150	13	0.8	23	13	160	13	
24	ALAGUPANDI	P	21	M	47	101	APPENDICECTOMY	I	0.9	21	16	210	12	0.9	20	12	213	12	0.9	20	14	218	12	
25	ARAVIND	P	21	M	43	106	APPENDICECTOMY	I	1	24	16	274	12	1	19	18	310	12	1	18	18	280	12	
26	MARIMUTHU	P	22	M	47	90	APPENDICECTOMY	I	0.7	29	20	150	14	0.7	30	21	214	14	0.7	30	21	230	15	

27	AYYANAR	P	20	M	50	93	APPENDICECTOMY	I	0.9	24	11	234	12	0.9	25	13	244	12	0.9	25	13	264	12	
28	SIVAKUMAR	P	21	M	48	94	APPENDICECTOMY	I	1	26	14	301	13	1	21	14	318	14	1	22	14	316	13	
29	CHELLAKANNU	P	39	M	56	103	APPENDICECTOMY	I	1.1	18	15	235	12	1.1	19	14	258	12	1	20	14	264	13	
30	PALANIAMMAL	P	35	F	49	107	APPENDICECTOMY	I	0.8	16	16	186	13	0.7	16	18	260	13	0.7	16	19	206	13	

MASTER CHART (ISOFLURANE WITH N-ACETYL CYSTEINE)

S.No.	name	group	age	sex	wt	duration	typeofsur	asa	prebili	preast	prealt	preldh	preptt	post1bili	post1last	post1alt	post1ldh	post1ptt	post24bili	post24ast	post24alt	post24ldh	post24ptt	Complication
1	MUTHUVEERIAH	N	50	M	70	128	**HERNIOPLASTY**	II	0.6	36	18	103	11	0.5	36	17	113	11	0.6	38	16	113	11	
2	MALAR	N	23	F	47	100	APPENDICECTOMY	I	0.7	42	22	106	12	0.8	45	24	109	13	0.8	46	22	109	13	
3	VIJAYAKUMAR	N	50	M	64	118	**HERNIOPLASTY**	II	0.8	46	33	141	12	1	40	31	150	12	0.8	38	36	160	12	Hypoter & Ras
4	CHINNASAMY	N	40	M	50	117	APPENDICECTOMY	I	0.9	18	17	210	13	0.9	16	25	213	13	0.9	18	26	218	13	
5	SAIBU NISHA	N	45	F	55	103	APPENDICECTOMY	II	0.7	16	18	274	11	0.7	19	18	310	12	0.7	20	20	280	12	Nause
6	DEEPAN	N	26	M	57	96	APPENDICECTOMY	I	1	18	41	143	12	1	17	38	136	12	1	17	36	131	12	
7	NAVEEN KUMAR	N	26	M	47	97	APPENDICECTOMY	I	0.9	20	23	106	13	0.9	21	28	109	13	0.9	21	22	116	13	
8	KARTHIK	N	27	M	43	93	APPENDICECTOMY	I	1	16	35	152	11	1	19	25	154	12	1	17	28	169	12	
9	SUNDARAM	N	30	M	42	102	APPENDICECTOMY	I	0.7	22	40	126	12	0.8	23	38	132	13	0.8	26	32	128	13	Hypoter
10	KUMAR	N	21	M	54	114	APPENDICECTOMY	I	0.7	28	18	186	13	0.7	32	17	260	12	0.7	33	18	206	12	
11	APARNA	N	21	F	58	95	APPENDICECTOMY	I	0.9	38	18	132	12	0.9	36	20	138	12	0.9	42	22	140	12	
12	VIJAYA	N	40	F	47	99	APPENDICECTOMY	I	0.8	35	28	148	14	0.8	40	22	164	14	0.8	40	38	154	13	
13	KAVITHA	N	26	F	59	94	APPENDICECTOMY	I	1	45	48	109	10	0.9	46	36	112	11	1	42	46	116	10	Nause
14	VANATHI	N	35	F	61	113	APPENDICECTOMY	I	0.9	22	14	133	12	1	28	18	119	13	0.9	32	18	111	12	
15	ANUSIYA RANI	N	36	F	68	130	**HERNIOPLASTY**	I	1	27	52	186	13	0.9	32	50	260	13	0.9	28	52	206	13	
16	SELVAM	N	25	M	49	95	APPENDICECTOMY	I	1	18	11	143	14	1	21	13	136	14	1	20	13	131	14	Hypoter
17	SATHISH KUMAR	N	25	M	56	95	APPENDICECTOMY	I	0.7	13	12	106	13	0.7	14	13	109	14	0.7	14	13	116	13	
18	JEEVA	N	40	M	48	91	APPENDICECTOMY	I	0.6	30	14	152	12	0.6	31	12	154	12	0.6	30	12	169	12	
19	MUTHU	N	25	M	47	101	APPENDICECTOMY	I	0.9	24	18	126	12	1	23	15	132	12	1	23	15	128	12	Nause
20	CHINNASAMY	N	34	M	57	100	APPENDICECTOMY	I	0.8	14	13	186	13	0.8	17	15	260	14	0.8	16	13	206	13	
21	JAYAKUMAR	N	25	M	63	126	**HERNIOPLASTY**	I	0.9	17	21	10	14	0.9	18	24	113	12	0.9	18	23	113	14	
22	THOMAS	N	40	M	48	130	**HERNIOPLASTY**	II	0.7	21	11	106	12	0.7	20	12	109	12	0.7	19	12	109	12	

23	SIKKANDER	N	27	M	43	85	APPENDICECTOMY	I	0.9	18	13	141	13	0.9	19	17	150	12	0.9	20	17	160	13	Hypoter
24	JEYALAKSHMI	N	25	F	45	89	APPENDICECTOMY	I	1	26	19	210	14	1	24	20	213	14	1	24	21	218	14	
25	SOUNDARAJAN	N	31	M	47	90	APPENDICECTOMY	I	0.8	11	16	274	13	0.8	14	17	310	13	0.7	14	15	280	12	
26	MOORTHY	N	38	M	57	96	APPENDICECTOMY	I	0.8	27	19	150	12	0.8	29	17	214	12	0.9	30	18	230	12	Nause
27	SARAVANAN	N	22	M	52	92	APPENDICECTOMY	I	0.7	15	17	234	14	0.7	13	20	244	14	0.7	13	20	264	13	
28	PANCHAVARNAM	N	21	F	50	100	APPENDICECTOMY	I	0.9	18	23	301	13	1	16	22	318	13	1	16	22	316	12	Hypoter
29	NANDA KUMAR	N	22	M	55	105	APPENDICECTOMY	I	0.8	20	21	235	14	0.8	15	20	258	14	0.8	14	20	264	14	
30	SUBBIAH	N	32	M	45	97	APPENDICECTOMY	I	1	19	20	186	12	1	26	19	260	12	0.9	27	19	206	12	Rash Urtica

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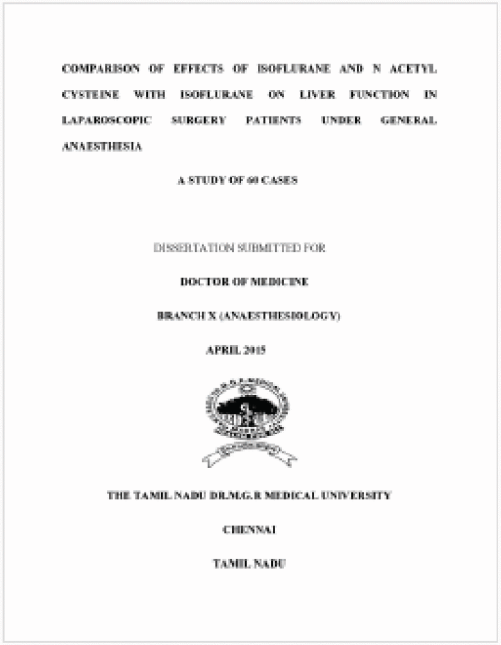

COMPARISON OF EFFECTS OF ISOFLURANE AND N ACETYL CYSTEINE WITH ISOFLURANE ON LIVER FUNCTION IN LAPAROSCOPIC SURGERY PATIENTS UNDER GENERAL ANAESTHESIA

A STUDY OF 60 CASES

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH X (ANAESTHESIOLOGY)

APRIL 2015

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

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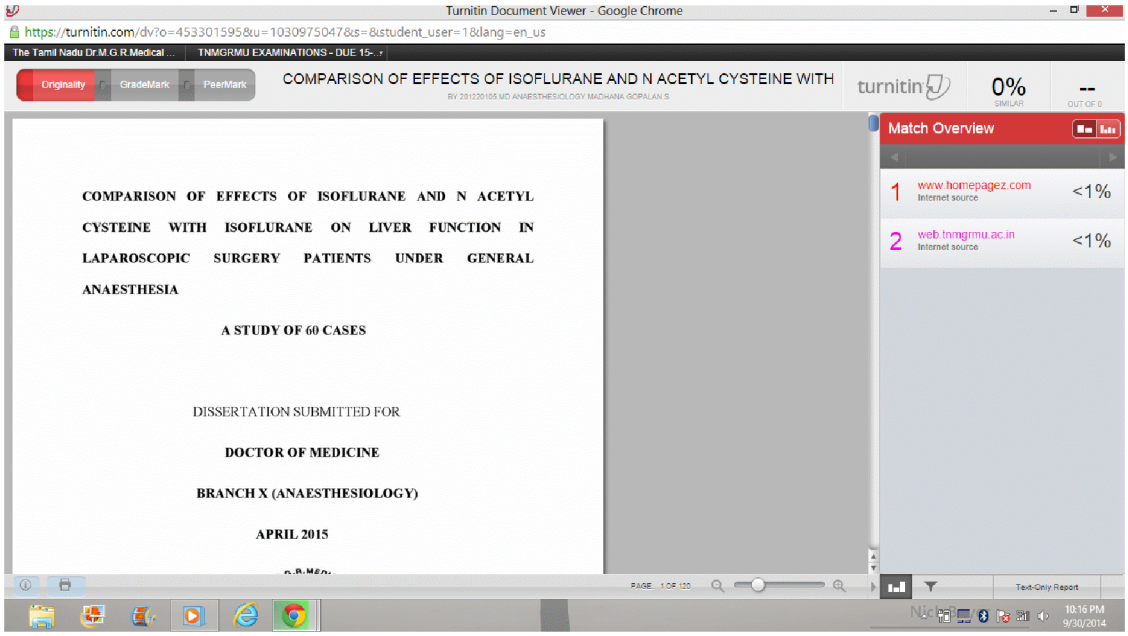
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Institutional Review Board / Independent Ethics Committee.
Capt. Dr.B. Santhakumar, M.D., (F.M.,) deanmdu@gmail.com
Dean, Madurai Medical College &
Govt Rajaji Hospital, Madurai 625020. Convenor

Sub: Establishment-Govt. Rajaji Hospital, Madurai-20-
Ethics committee-Meeting Minutes- for March 2014
Approved list - Regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held on 05.03.2014, Wednesday at 10.00 am to 12.00.noon at the Auditorium, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

1.Dr.V. Nagarajan, M.D., D.M (Neuro) Ph: 0452-2629629 Cell.No 9843052029 nag9999@gmail.com	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2. Dr.Mohan Prasad , M.S M.Ch Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology(Retired) D.No.32, West Avani Moola Street, Madurai -1	Member Secretary
3. Dr. Parameswari M.D (Pharmacology) Cell.No.9994026056 drparameswari@yahoo.com	Director of Pharmacology Madurai Medical College	Member
4. Dr.S. Vadivel Murugan, MD., (Gen.Medicine) Cell.No 9566543048 svadivelmurugan_2007@rediffmail.com	Professor& H.O.D of Medicine Madurai Medical College	Member
5. Dr.S. Meenakshi Sundaram, MS (Gen.Surgery) Cell.No 9842138031 drsundarms@gmail.com	Professor & H.O.D of Surgery Madurai Medical College	Member
6. Mrs. Mercy Immaculate Rubalatha, M.A., Med., Cell. No. 9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's quarters, Gandhi Museum Road, Thamukam, Madurai-20	Member
7. Thiru..Pala. .Ramasamy , BA.,B.L., Cell.No 9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72.Palam Station Road, Sellur, Madurai -2	Member
8. Thiru. P.K.M. Chelliah ,B.A Cell.No 9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20	Member

The following Projects was approved by the committee.

Name of P.G.	Course	Name of the Project	Remarks
Dr.S.Madhana Gopalan	PG in MD (Anaesthesiology), Madurai Medical College and Government Rajaji Hospital, Madurai	A study on effects of N-acetyl cysteine on hepatic function during isoflurane Anaesthesia.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman

29.3.14
DEAN/Convenor
Govt. Rajaji Hospital,
Madurai- 20.

To
The above Applicant
-thro. Head of the Department concerned

forwarded to Dr Madhana Gopal

DIRECTOR
INSTITUTE OF ANAESTHESIOLOGY
Madurai Medical College &
Govt. Rajaji Hospital
Madurai-625 020